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AN "ALZHEIMER'S PROFILE" AMONG THE SUBTESTS OF THE WECHSLER MEMORY SCALE--REVISED?

BY

DAVID W. ROWE

A dissertation submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

in

SCHOOL PSYCHOLOGY

DEPARTMENT OF EDUCATIONAL PSYCHOLOGY

EDMONTON, ALBERTA

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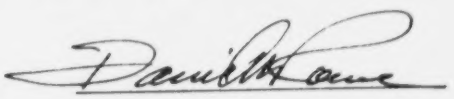

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The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance, a dissertation entitled *An Alzheimer's Profile Among the Subtests of the Wechsler Memory Scale--Revised?* submitted by David W. Rowe in partial fulfilment of the requirements for the degree of Doctor of Philosophy in School Psychology.

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ABSTRACT

The medical and psychological assessment records of 210 elderly patients who had undergone a comprehensive neuropsychological assessment which included the Wechsler Memory Scale--Revised (WMS-R) were recovered and subjected to analysis to examine whether a profile of memory impairment could be found that would have clinical utility in the early diagnosis of dementia of an Alzheimer's type (DAT). An Impairment Index was calculated from assessment measures other than the WMS-R, and patients were grouped by diagnostic category and degree of impairment--normal to mild or moderate to severe. Discriminant function analysis demonstrated that while overall accuracy of classification was low at 44%, the subtests of the WMS-R yielded in the best case 59.1% correct classification (sensitivity) for patients with mild possible/probable DAT. Despite low overall accuracy, specificity was high ranging from a minimum of 87.9% to a maximum of 94.5% with different patient groupings. The profile identifying DAT individuals showed impaired memory functions relative to overall cognitive impairment, as determined by the Impairment Index, and impaired verbal memory function relative to general memory function. A number of studies have suggested that visual memory as well as verbal memory is impaired in early DAT, and the question is raised whether the failure to find deficits of visual memory comparable to those found with verbal memory is a function of the disease process or an insensitivity of the WMS-R visual memory subtests.

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AN "ALZHEIMER'S PROFILE" AMONG THE SUBTESTS OF THE WECHSLER MEMORY SCALE--REVISED?

CHAPTER I

INTRODUCTION

As global demographics change and populations, especially in developed nations, age, dementia is an increasing health care problem. It is the fourth major cause of death in the developed world after heart disease, cancer, and stroke (Hardy & Allsop, 1991). The identification, treatment and/or management of dementias has become a major health care issue. Estimates of the prevalence of dementia for the population over 65 is approximately three percent. By age 85 and beyond, the estimated prevalence ranges from approximately 10% to nearly 50%. In the populations of the developed world, the major etiologies of dementia are Alzheimer type dementia and arteriosclerotic dementias, multi-infarct or stroke-related, Binswanger's, and other less-well-defined vascular dementias. In addition to these cortical dementias, there are a number of subcortical dementias. Parkinson' disease is frequently identified as the most prevalent subcortical dementia; however, there is considerable debate whether Parkinson disease, of itself, produces a true dementia or the dementia observed in some parkinsonian patients results from a co-existing primary or Alzheimer type dementia. Dementia may arise as well from a number of metabolic imbalances, drug effects, tumors, obstructive or normal pressure hydrocephalus, subdural hematoma, transient ischemic attacks and some other causes. Such dementias, many of which are "reversible", are, for the most part, identified with reasonable accuracy and treated, and they are not a concern of this research.

In addition to the dementias identified, there is considerable related literature that concerns itself with *pseudodementia*. Pseudodementia is memory loss and apparent cognitive decline that may arise with depression, often a "masked depression", in elderly individuals. Some of the dementia literature suggests that it is difficult to distinguish between pseudodementia and a true dementia. However, it appears that such is the case primarily when there is

an attempt of differential diagnosis on the basis of screening instruments or inadequate neuropsychological assessment; though the picture is complicated in early dementia where a clinically significant depression is co-existent. Pseudodementia is, then, only a minor consideration in the research to be undertaken in this study.

This investigation is concerned with the early identification of dementia; specifically dementia or senile dementia of an Alzheimer type. Early differential diagnosis of the etiology of a dementia offers the best possibilities for treatment of that dementia. At present, the best that can be offered the victims of Alzheimer type dementia is benevolent management that provides some relief to the afflicted individual and his or her family. While there is diligent, sophisticated pharmacological research seeking a treatment for Alzheimer's disease, there is little evidence arising from current research that the cognitive losses arising from primary degenerative dementia, or the other major dementias, are *reversible*; however, such losses may be *arrestable*. A dementia that is arrestable, but not reversible, yields a treatment conundrum: if dementia is to be successfully treated, it must be identified and treated before it has progressed to a true dementia.

The new *Diagnostic and Statistical Manual of the American Psychiatric Association, Fourth Edition* (1994) no longer provides diagnostic for criteria for Dementia as a separate nosological entity, but rather specifies the diagnostic criteria for each of Dementia of the Alzheimer's Type, Vascular Dementia, Dementia Due to HIV Disease, Dementia Due to Head Trauma, Dementia Due to Parkinson's Disease, Dementia Due to Huntington's Disease, Dementia Due to Pick's Disease, Dementia Due to Creutzfeldt-Jakob Disease, Dementia Due to Other General Medical Conditions, Substance-Induced Persisting Dementia, and Dementia Due to Multiple Etiologies, and provides for Dementia Not Otherwise Specified when the clinician is unable to determine a specific etiology (p. 133). However, because this investigation is concerned with the differential diagnosis of dementia when the etiology is unknown or uncertain, the description of dementia per se in the earlier version of the Diagnostic and Statistical Manual is more illustrative of the general meaning of the term.

The *Diagnostic and Statistical Manual of the American Psychiatric Association, Third Edition--Revised* (1987) defines Dementia as

A. Demonstrable evidence of impairment in short- and long-term memory. Impairment in short-term memory (inability to learn new information) may be indicated by an inability to remember three objects after five minutes. Long-term memory impairment may be indicated by inability to remember past personal information (e.g., what happened yesterday, birthplace, occupation) or facts of common knowledge (e.g., past Presidents, well-known dates).

B. At least one of the following:

(1) impairment in abstract thinking, as indicated by inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks
(2) impaired judgment, as indicated by inability to make reasonable plans to deal with interpersonal, family, and job-related problems and issues
(3) other disturbances of higher cortical function, such as aphasia (disorder of language), apraxia (inability to carry out motor activities despite intact comprehension and motor function), agnosia (failure to recognize or identify objects despite intact sensory function), and "constructional difficulty" (e.g., inability to copy three-dimensional figures, assemble blocks, or arrange sticks in specific designs)
(4) personality change, i.e., alteration or accentuation premorbid traits

C. The disturbance in A and B significantly interferes with work or usual social activities or relationships with others.

D. Not occurring exclusively during the course of Delirium.

E. Either (1) or (2):

(1) there is evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
(2) in the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder, e.g., Major Depression accounting for cognitive impairment
(American Psychiatric Association, 1987, p. 107)

If, then, dementia is defined by memory and other cognitive impairment having reached a degree of severity that adequate occupational and social functioning are disturbed and the present best hope is to arrest the cognitive declines but not reverse them, the gains to be made from treatment do not yield a fully functional individual. For a pharmacotherapy, or other therapy, that only arrests cognitive decline to be most efficacious, the development of

a set of criteria that will determine the *probability* of an individual developing a dementia must be identified so that treatment may begin prior to the development of cognitive changes that incapacitate an individual occupationally and socially.

As will be demonstrated in depth in the pages to come, memory decline is the hallmark of dementia in general and in dementia of an Alzheimer type (DAT) and senile dementia of an Alzheimer type (SDAT) in particular. It seems a reasonable working hypothesis, then, that research might define a pattern of memory change in individuals who will develop an Alzheimer type dementia (AD) that is different from the pattern of memory change observed in normal individuals of the same age. While there is a body of research literature that suggests that AD is not a homogeneous disorder, i.e., that there are subtypes of AD, the greater body of research appears to suggest that the initial manifestation of the disorder, regardless of subtype, is memory loss. A pattern of memory change that differs from normal age-related memory change is, however, a primary feature of other dementias from which AD is to be differentiated; hence, any pattern of memory change in AD must be differentiable not only from normal age-related memory change, but also from memory changes in other dementias.

The Wechsler Memory Scale--Revised (Wechsler, 1987) is a widely used clinical instrument for the assessment of memory. The 13 subtests of the Wechsler Memory Scale--Revised (WMS-R) yield five indexes: General Memory, Attention/Concentration, Verbal Memory, Visual Memory, and Delayed Recall. The purpose of this investigation was to determine whether analysis of performance on the WMS-R subtests or a subset of those subtests would yield a distinctive profile of memory changes that will contribute to a reliable differential diagnosis of dementia of the Alzheimer type.

CHAPTER 2

REVIEW OF THE LITERATURE--THE SCOPE OF THE PROBLEM

PREVALENCE

An advertisement in the September 1992 issue of *Scientific American* by the Pharmaceutical Manufactures Association, referring to Alzheimer's disease in the United States, states "over 4 million people suffer from it," and asserts that it costs " over $88 billion a year for institutional and homecare." While that source may be viewed suspiciously, Cohen (1988) reports similar dollar costs. He reports that AD and related disorders are considered responsible for at least one-half of the admissions to nursing homes in the United States with an estimated cost in excess of $14 billion (1985 dollars) for institutional care alone. The estimates of total direct costs, community home care, and nursing home care, plus indirect costs, premature death and, loss of productivity, come to approximately $88 billion. In either case, the economic cost of Alzheimer's disease is staggering.

Estimates of Prevalence--United States

In the same issue of *Scientific American* Dennis Selkoe reports that the 1992 "Framingham study " (Bachman et al. 1992), which repeatedly assessed the health of a large group of subjects, estimated the prevalence of dementia as follows: age 60-64, 0.4%; age 65-69, 0.9%; age 70-74, 1.8%; age 75-79, 3.6%; age 80-84, 10.5%; and age 85-93, 23.8%. Selkoe then contrasts that study with a study by D.A. Evans of Harvard Medical School (Evans et al., 1989). The Framingham-Evans studies demonstrate the broad range of estimates of the incidence of Alzheimer's disease (AD) in the demented population. The range of those estimates is presented by three age groups giving Framingham study verses the Harvard Medical School Study: 65-74 years, 0.5% vs. 3.0%; 75-84 years, 4.1% vs. 18.7%; and 84+ years, 13.1% vs. 47.2%.

According to Evans et al. the probable discrepancy between the estimates lies in methodology. They point out that most studies of Alzheimer's disease have been conducted among outpatients referred for evaluation to some

institution, i.e., tertiary-care medical centres, chronic-care institutions or psychiatric hospitals, while their own study was among individuals 65 years of age and older in a defined community.

Evans and colleagues conducted their study in East Boston, Mass. within a working-class community of approximately 32,000 people. The Evans group determined from census data that there was a population of 4485 persons over age 65 in the community. A population survey of brief memory testing was conducted of 3623 persons, approximately 81% of the total over age 65 population. They divided their sample results into three groups, Good Memory Performance, Intermediate Memory Performance, and Poor Memory Performance. The brief memory performance measure involved recall of a brief story composed of three short sentences each containing two ideas and included immediate and delayed (approximately 2-minutes) recall. The maximum score was 6. The Good Memory Performance Group was composed of those who had zero to two errors on immediate recall. The Poor Memory Performance Group was composed of those with four or more errors on immediate recall and six errors or no correct recall on delay. The Intermediate Memory Performance Group was composed of those who scored between the Good and Poor Groups.

From the 2137 persons in the Good Memory Performance Group, 170 individuals were randomly selected for Stage Two Clinical Evaluation. One hundred-one persons from the 1108 in the Intermediate Memory Performance Group and 196 persons of the 378 in the Poor Memory Performance Group were selected for further evaluation. The Stage Two clinical evaluation included neurological, neuropsychological, psychiatric and laboratory assessment. The diagnostic criteria for "Alzheimer's disease" was "consistent with the criteria for the clinical diagnosis of probable Alzheimer's disease developed by the Joint Work Group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association as well as those for the *Mental Disorders, Third Edition*, of the American Psychiatric Association" (Evans et al., 1989, p. 255). Analysis of the data obtained indicated that for the community surveyed the prevalence rate for probable AD was 11.6% for the population over the age of 65 years. In discussing the limitations of their study, Evans et al. note that because the population they studied included *only noninstitutionalized*

individuals, it is likely that the prevalence of both cognitive impairment and Alzheimer's disease would have been higher had such individuals been included.

Leon Thal (1988) working with the United States 1980 population census noted that 11% or 25.5 million of the 232 million persons in the country at that time were more than 65 years old. Fifteen percent or 3.8 million of those were demented. Of that population, one half of the cases were secondary to Alzheimer's disease. Estimates at that time anticipated almost 3 million people with AD by 1988. Thal's estimates of prevalence were based on patient populations. He reported that among 222 patients at three neurology services, AD and SDAT accounted for approximately 50% of the cases of dementia. Patients with depression or other psychiatric disorders constituted about 10% of the cases while dementias resulting from vascular disorders accounted for 8%. A number of illnesses and conditions--normal pressure hydrocephalus, alcoholism, intracranial mass lesions, drug toxicity, infections, and metabolic disorders--were responsible for the balance of cases.

In another study in which 200 patients were evaluated for dementia with CT scan, 75% were said to have dementia of Alzheimer's type. Ten percent were identified as dementia secondary to drugs and 7.5% were reported as depressed with a "handful" of other diseases accounting for the remaining 7.5%. In a third study, 375 patients were assessed. Of those 70% were identified as SDAT. Nine percent had both AD and a vascular disease, and 5% were demented due to vascular disease alone. The remaining 16% were accounted for through 15 other diagnoses (Thal, 1988).

Terry and Katzman (1983) report the incidence of severe dementia, on the basis of community surveys, averages between 4% and 5% for *severe* dementia and about 10% for mild to moderate dementia in the population over 65 years old. In general, severe dementia has, in the surveys used, meant cognitive impairment that precludes independent living while mild to moderate dementia has indicated some ability to live at least semi-independently. At those levels of incidence, they estimated that in the United States in 1983 there would be 1.3 million cases of severe dementia and 2.8 million with mild to moderate dementia. The incidence and prevalence of dementia increase with age. Terry and Katzman report that the incidence of dementia at age 65 is 0.01% per year but that it rises to 3.5% per year by age 85. The prevalence

of severe dementia increases from less than 1% at ages 65 to 70 to over 15% by age 85. They note, parenthetically, that the fastest growing group in the U.S. population is the over age 85 cohort and that the mortality in that group declined 20% in the previous decade.

Estimates of Prevalence--Canada

Canadian estimates of the prevalence of DAT do not differ greatly from the more conservative of the American estimates. Gautrin, Froda, Tetreault, and Gaureau (1990) of the University of Quebec drew upon Finnish studies (Mölsa et al.; Sulkava et al., cited in Gautrin et al.) to estimate the number of Canadians who would be affected by AD or SDAT over the period from 1986 to 2031. They point out that the common practice in the medical community is to assume that 2.5% of individuals 65 years of age and older are afflicted with severe SDAT. Gautrin et al. argue that the 2.5% is but a crude estimate of the prevalence of SDAT in the 65 years and older population. They note that the estimate is derived indirectly from two different studies. The first study (Tomlinson et al. cited in Gautrin et al.) was based on a series of autopsies on the brains of 50 demented elders of which half the brains showed Alzheimer type lesions. The second study (Mortimer cited in Gautrin et al.) reported that on the basis of ten selected studies the incidence of dementia for the group aged 65 years and greater was 5%. If one-half of that group are true Alzheimer disease victims, then the incidence of Alzheimer's disease in the 65 years and older group is 2.5%.

The University of Quebec researchers observe that there are difficulties with the approach taken. They point out that the brains autopsied in the first study were not derived from a random sample of demented old people; hence, the 50% figure may not apply to all populations of the demented elderly. They note that the prevalence of AD is known to vary with age, as is demonstrated with the American studies already discussed, so the 2.5% figure is not particularly informative. They observe, further, that many of the reported prevalence studies were carried out prior to 1976 and that the criteria for the diagnosis of AD has significantly changed in the meanwhile. Somewhat ironically, it seems, given that the studies on which they based their projections were Finnish, they complain that the studies on which the 5% prevalence rate was based were not carried out in North America. In

establishing the rationale for their study, Gautrin et al. (1990) assert that "No population based prevalence study has been conducted in a large community either in Canada or the United States (p. 163)." Given the study by Evans et al. (1989) reported above, that statement is clearly incorrect, though, in fairness, it should be observed that the Gautrin et al. paper was submitted to the Canadian Journal of Psychiatry in July of 1986, revised July 1989, and only published in March of 1990.

Gautrin et al. (1990) argue for the Finnish studies on the basis that they (a) were relatively recent, (b) covered large populations, and (c) were mostly Caucasian in composition. Both studies, Mölsa et al. and Sulkava et al., on which they based their projections were designed to screen all demented persons in the population, and all suspected cases underwent a neurological examination; though one study (Mölsa et al.) used a community survey for case-finding while the other (Sulkava et al.) surveyed a random sample. The Mölsa et al. study included only moderately and severely demented subjects while the Sulkava et al. study restricted itself to severe cases of dementia and excluded persons with "mild cognitive disturbances" and "circumscribed neuropsychological symptoms" including aphasia and apraxia. (Unfortunately, the exclusion of individuals manifesting aphasia may have significantly lowered the incidence of DAT as studies to be presented in a subsequent section of this review will show that in as many as 44% of cases of DAT, aphasia is the initial symptom (Capitani, Della Salla, & Spinnler, 1990). The two Finish studies yielded significantly different results: in the 65 - 74 age group, the Mölsa et al. study found a prevalence rate of 0.36% while the second study found a prevalence rate of 1.70%; in the 75 - 84 age group the rates were, respectively, 1.90 and 6.30%; and in the 85 and over group the rates were 6.30 and 14.80%. The Canadian researchers averaged the rates to obtain the following "Average Prevalence Rates": 65 - 74 years 1.0%; 75 -84 years 4.0%; and 85 and over 10.5%.

On the bases of the average prevalence rates obtained, Gautrin, et al. (1990) provided the projected numbers of AD cases in the Canadian population for each five-year period from 1986 to 2031 for each of the three age groups (p. 163). Three of those periods are reported here in Table 1.1.

Table 1.1

Projected cases of AD in the Canadian Population for 1991, 2001, and 2031 (Gautrin et al., 1990)

	Census Year		
Age Group	1991	2001	2031
65 - 74	18,884	21,128	39,065
75 - 84	40,544	53,892	98,484
85 and over	28,499	44,467	78,298
Total	87,893	119,487	215,847

Table 1.2 contrasts the above projections with projections for the numbers Canadians with AD in the same years based on the prevalence rates found Evans et al. Harvard Medical School (1989) and "Framingham" (Bachman et al., 1992) studies.

The projections for Canadian AD cases derived from the Bachman et al. study closely approximate those of Gautrin et al. The Harvard Medical School Study yields, on the other hand, case projections approximately 4.3 times greater than the other two studies. A major part of the difference lies in the inclusion of mild dementia cases in the Evans et al. study while only moderate and severe cases were included in the Bachman et al. study. Other methodological differences also contributed to differences in prevalence rates. Bachman et al. point out that other studies have, for example, confined selection of subjects for further evaluation to those who did poorly on population

Table 1.2

Projected Cases of AD in the Canadian Population for 1991, 2001, and 2031 on the basis of Harvard Medical School Study (Evans et al., 1990) and "Framingham Study" (Bachman et al.,1992)

	Harvard Med. School Census Year			"Framingham" Census Year		
Age Group	1991	2001	2031	1991	2001	2031
65 - 74	56,652	63,384	117,195	9,442	10,564	19,532
75 - 84	189,590	251,945	460,413	41,558	55,239	100,946
≥85	128,110	199,890	351,192	35,556	55,478	97,686
Total	374,352	515,219	928,800	86,556	121,281	218,164

screening instruments, included institutionalized subjects, or used different criteria for classification. Evans et al. acknowledge that their prevalence rates are likely underestimates and suggest that they be treated as minimum rates. The Evans group also notes that in their study only 55.6% of dementia cases were classified as probable SDAT while in the Harvard Medical School study "nearly all cases . . . were classified as probable SDAT" (p. 118), and indeed the Bachman group found that among those with moderate to severe dementia 84.1% had Alzheimer's disease alone and another 7.1% had Alzheimer's disease in conjunction with another cause of dementia while only 8.8% had a cause of dementia other than AD. Bachman et al. argue that the high number of AD cases is to some extent due to the fact that individuals with other diseases causing dementia tend to be hospitalized or institutionalized earlier and removed from the community. Despite being significantly higher than the other estimates of prevalence reported in recent studies, Bachman et al. suggest that their prevalence rates are also underestimates because cases in which AD coexists with some other disease are excluded and because institutionalized subjects were not included.

Prevalence Differences between Males and Females

Only the Framingham study of Bachman et al. (1992), among recent population based studies, comments on the difference in prevalence between men and women. Of 90 cases of definite dementia identified from among 2,180 individuals 61 years and older, the prevalence of dementia was 30.5/1,000 for men and 48.2/1000 for women. The prevalence of dementia was significantly ($p < 0.001$) related to age for both men and women. Among individuals 75 years and older the prevalence of dementia was significantly ($p < 0.03$) greater for women than men. In that age group, the prevalence for women was 120.5/1,000 as compared with 68.0/1,000 for men, a ratio of 1.8. In 50 cases studied, the prevalence of probable SDAT was 11.7/1,000 for men and 30.1/1,000 for women. In the age group older than 75 years, the prevalence of SDAT increased to 78.2/1,000 for women and 28.0/1,000 for men, a ratio of 2.8. While these rates appear to reflect a greater susceptibility to SDAT among women, the authors suggest that there may be other explanations for the increased prevalence among women. Following White et al. (1986 cited in Bachman et al.,

1992), they speculate that older men are more likely to have younger spouses who continue to care for them during a time in which they would otherwise come to attention because of their cognitive impairment. An alternate explanation is raised that women with dementia may survive longer than men with dementia with the result that a greater number of women with dementia will be detected in a prevalence study.

Prevalence--North America

Review of prevalence studies fails to yield a definitive estimate of the prevalence of AD in North American populations. The studies described yield rates ranging from 0.5% to 3.0% for the 65 -74 year-old group; from 4.0% to 18.7% for the 75 - 84 year-old group; and from 13.1% to 47.2% for the 85 year and older group. The primary difference in rates arises from the inclusion or exclusion of cases of mild dementia. A body of work by Leonard Berg and his colleagues at the Memory and Aging Project, and Alzheimer's Research Center at the Washington University Medical School in St. Louis (L.Berg, 1988; Berg et al, 1984; Rubin & Kinsherf, 1989; Rubin, Morris, Grant, & Vendega, 1989; Storandt, Botwinick, Danziger, Berg, & Hughes, 1984; Storandt & Hill, 1989) demonstrates that many cases of early dementia will progress to moderate and severe dementia of an Alzheimer's type. The exclusion of mild dementia undoubtedly leads to an underestimate of the prevalence of DAT, and it is probable that the higher estimates best approximate the actual prevalence of the disorder in North America. However, even considering only the estimates of prevalence that include mild cases of dementia, a broad band of prevalence estimates is generated. Using the estimates of Sulkava et al. (cited in Gautrin et al, 1990) and those of the Harvard Medical School study (Bachman et al., 1989) range of the estimates is from 1.7% to 3.0% for the 65 - 74 year-old group; 6.3% to 18.7% for the 75 - 84 year-old group; and 14.8% to 47.2% for the 85 year-old and greater group.

Pursuing the lead of Gautrin et al. in which the two estimates were averaged, the following rates of prevalence are obtained using the studies by Sulkava et al. and Bachman et al.: 65 - 74 years 2.4%; 75 - 84 years 12.5%; 85 and older 31%. While these estimates yield less than the "4 million" cases of Alzheimer's disease suggested by the Pharmaceutical Manufactures Association, they do suggest a major health care problem with almost one-third

of the 84 years and older group, the fastest growing group in the North American population, and over one-twelfth of the next oldest group suffering SDAT. Reckoning the United States population as ten times that of the Canadian population, the above averages suggest that in the second year of the 21st century--2001--there will be 3,504,020 cases of DAT in the U.S. with another 350,402 cases in Canada for a North American total of approximately 3,854,000 persons all of whom will require either institutional care or the near total time of another individual for daily care.

THE ETIOLOGY OF ALZHEIMER'S DISEASE

The Cholinergic Hypothesis

A primary difficulty in the diagnosis of AD arises from a deficit knowledge of the etiology of the disorder. Medical research has not been able to identify a pathogen, whether virus or environmental toxin, or changes in some physiological or metabolic process that lead to the lesions characteristic of AD. Neither is there agreement on the means by which some virus or toxin gains access to cerebral tissue nor agreement on which brain region is the first to be affected by the etiologic agent. A number of hypotheses have, however, been advanced which have evoked substantial interest and research. Primary among those is the cholinergic hypothesis. Bartus, Dean, Pontecorvo and Flicker (1985) define the cholinergic hypothesis as follows:

> Stated in its most simple and direct terms, the cholinergic hypothesis asserts that significant, functional disturbances in cholinergic activity occur in the brains of aged and especially demented patients, these disturbances play an important role in the memory loss and related cognitive problems associated with old age and dementia, and proper enhancement or restoration of cholinergic functioning may significantly reduce the severity of the cognitive loss (p. 332).

They add that the cholinergic hypothesis says nothing about the etiologic factors; that it does not address other roles of cholinergic dysfunction in other neurobehavioral disturbances; and that it does not argue the exclusive involvement of the cholinergic system in age-related memory loss. There is not complete agreement on mechanisms through which the cholinergic system is

involved in dementia or age-related memory loss. Neary et al. (1986) point out that several independent groups of researchers have found a reduction in the activity of choline acetyl-transferase (CAT), an enzyme which catalyses the synthesis of acetylcholine (ACh), in the cerebral cortex of patients with AD. The research further shows that the post-synaptic muscarinic receptors are not greatly affected.

Neary et al. (1986) suggest that those findings raise the possibility of therapy for AD patients by the use of agents enhancing the activity of the cholinergic system. Neary and colleagues studied 17 patients with histologically proven (through biopsy) AD. They found that the severity of dementia was highly correlated with pathological changes (cell loss, reduction of nuclear and nucleolar volume and cytoplasmic RNA content) in the large cortical neurons and, to a lesser degree, with cortical senile plaques (SP) and neurofibrillary tangles (NFT) and reduction of ACh synthesis but *not* with reduction in CAT activity. They also found a significant correlation between CAT activity and SP frequency thereby, in their evaluation, linking changes in the subcortical projection system of the nucleus basalis with cortical pathology. Neary et al. report stronger correlations between chemical, pathological, psychological measures, and ACh synthesis than measures of CAT, and suggest that measures of ACh synthesis appear to be the more sensitive index of the "physiologically active pool of ACh in the cortex" (p. 236). They argue that the reduction in presynaptic cholinergic activity found in their study likely reflects the retrograde degeneration of ascending cholinergic tracts resulting from the failure of cholinergic cells in the nucleus basalis. They argue, further, that the formation of senile plaques probably reflects changes in the synaptic endings of neurons arising within and projecting from the nucleus basalis.

Sahakian, Jones, Levy, Gray, and Warburton (1989) focused their research on the nicotinic receptors in the cholinergic system. They hypothesized that it should be possible to obtain at least partial improvement in memory and other cognitive functions in DAT through the administration of nicotine, a cholinergic receptor agonist. Their results yielded significant group, DAT patients and controls, differences in accuracy of detection/ sensitivity index, a significant and marked quickening of reaction time with DAT patients.

but no significant changes in short-term memory for either group. They concluded that nicotine improved attention and information processing but not short-term memory.

The cholinergic hypothesis is attractive because it suggests a means of treatment, namely the administration of cholinomimetics. Bartus et al. (1985) report that attempts to use cholinomimetics can be classified into one of three approaches: precursor therapy, anticholinesterase treatment, and muscarinic receptor agonist treatment. Of these, the cholinergic precursors have, because of their relative safety, spawned the majority of studies. Research groups have administered a number of different nootropic compounds: oxiracetam (Maina et al.,1989; Villardita, Grioli, Lomeo, Cattaneo, & Parini, 1992); physostigmine (Jenike, Albert, Heller, Gunther, & Goff, 1990); and tacrine (Davis et al, 1992; Farlow, Gracon, Hershey, Lewis, Sadowsky, & Dolan-Ureno, 1992) to name but a few of the compounds and fewer of the studies.

Oxiracetam is a derivative of GABA and is believed to increase acetylcholine at the synaptic level and is shown to "increase high-affinity choline uptake in the hippocampus, and to stimulate the utilization of acetylcholine in the cerebral cortex and hippocampus" (Villardita et al., 1992, p. 24). The oxiracetam studies have shown, in general, statistically significant improvements in favour of oxiracetam compared to a placebo. Those improvements have, however, not been clinically significant. In the Villardita et al. study, for example, the oxiracetam group (which included mild to moderately demented SDAT and MID patients) improved from a mean score of 18.5 ± 1.1 at Day 1 to 20.6 ± 1.1 at Day 90 on immediate recall of Rey's 15 Words Test while in the placebo group the change was from 18.8 ± 1.1 at Day 1 to 18.4 ± 1.1 at Day 90. On delayed recall of the same test the improvement in the treatment group was from 2.3 ± 0.3 to 2.8 ± 0.2 at Day 90 while the placebo group's scores were, respectively, 2.4 ± 0.3 and 2.5 ± 0.2. Such changes are clinically inconsequential.

The Maina et al. (1989) research team obtained similar clinically insignificant results with groups that included DAT, MID and mixed DAT-MID patients. At entry the oxiracetam group's (n = 141) Blessed Dementia Scale score was 10.7 ± 4.25 and at 12 weeks it was 9.0 ± 4.17; the placebo group's (n = 130) respective scores were 10.5 ± 4.20 and 10.3 ± 4.54. On the Newcastle Memory, Information and Concentration Scale, the treatment group's

scores had improved from 18.4 ± 7.34 at entry to 20.9 ± 6.93 at the 12th week. The placebo group's scores were 17.3 ± 7.06 at entry and 17.7 ± 7.54 at the 12th week. The Jenike et al. (1990) study with physostigmine with a small group (n = 12) of mildly to moderately impaired DAT patients in a double-blind crossover design found that individual responses to physostigmine were highly variable and intragroup differences were not significant. Both the tacrine studies reported were multicentre studies and involved large numbers of patients. The Davis et al. (1992) involved 623 patients with probable Alzheimer's disease and the Farlow et al. (1992) study involved 468 patients with DAT. Results were similar to those obtained with the oxiracetam research; statistically significant but not clinically significant improvements with tacrine.

The results of the "replacement" research has lead Growdon (1992) to the following observations:

> From a scientific point of view, the very modest effects of short-term tacrine administration indicate that enhancement of acetylcholine transmission is inadequate to reverse the signs and symptoms of Alzheimer's disease. Pending discovery of another neurotransmitter deficit that fully accounts for the dementia, it is now time to abandon simple replacement therapy and to develop treatments that can affect the fundamental mechanisms of neuronal degeneration. Further attempts to treat the disorder will follow strategies to restore neuronal function, protect neuronal survival, or prevent neurons from dying in the first place (Growdon, 1992, p. 1307).

Broken Barriers

Hardy, Mann, Wester, and Winblad (1986) suggest in a closely reasoned paper that the cerebral vessel amyloidosis common in AD arises in a defect in structure or function of the blood brain barrier. Neary et al. (1986) argue that the progression in the histopathology in AD likely reflects the retrograde degeneration of ascending cholinergic tracts due to the failure of cholinergic cells in the nucleus basalis, and that the formation of senile plaques (SP) probably reflects changes in the synaptic endings of neurons arising within and projecting from the nucleus basalis. Hardy et al. propose, conversely, that the site of the primary lesion is in the cerebral cortex,

most probably within the amygdala/hippocampus, and that the subcortical changes are secondary.

Hardy et al. (1986) offer the following in support of their position. They observe that all subcortical neurons affected in AD project to common areas of the cortex while non-cortically projecting cells appear to be unaffected. They suggest that it is particularly pertinent that cells of the ventral tegmentum are severely affected in AD but those of the substantia nigra are not. The cells of both the ventral tegmentum and the substantia nigra are dopaminergic, and they have close anatomical and embryological origins, but the cells of the ventral tegmentum project to the cerebral cortex and the amygdala while the cells of the substantia nigra project primarily to the striatum. They point out that cell loss from the locus caeruleus in AD does not appear to be uniform, and that the cell loss is greatest in the central parts of that nucleus that project to temporal and parietal cortical areas and least in the most rostral and caudal areas which project, respectively, to the frontal and occipital areas. Areas of the locus caeruleus projecting to the spinal cord, basal ganglia, and cerebellum show no significant cell loss. Hardy et al. (1986) observe, further, that the loss of cortical cholineacetyl-transferase is far greater than the loss of cells from the nucleus basalis, and that since the loss of synapses from the temporal cortex in AD averages 55% and the total cholinergic and monaminergic terminals within the cortex (at least in rodents, and they argue perhaps considerably less in humans) account, at most, for 10-15% of total synaptic endings "it is unlikely that a degenerative process primarily involving subcortical projection systems could, be itself, account for the magnitude of synapse loss recorded within the cortex" (p.493).

Hardy et al. argue that the increased CSF/serum ratios for IgG and albumin together with elevated albumin levels in patients with AD are consistent with increased permeability of the blood brain barrier. Such a "leak" in the blood brain barrier could allow neurotoxins or pathogens in circulation to be taken up by nerve cells. They are unable, on the basis of their research, to suggest a causative agent or agents.

Brun (1989) observes that several authors have found the basal temporo-limbic areas are involved earlier and more severely in DAT than are other brain areas, and that in later stages the postcentral parieto-temporal

neocortical areas are more severely involved than other parts of the cortex if other changes, gliosis, microcavitation and neuronal loss, as well as plaques and tangles are taken into account. He notes that spongiosis or microcavitation while not indicative of a viral infection in DAT does serve to separate DAT from normal aging which may include moderate numbers of senile plaques and tangles. Burn, with others (Hardy et al., 1986; Pearson et al. cited in Hardy et al., 1986), suggests that current research supports the hypothesis that the pathway for the etiological agent in AD is through olfactory pathways.

In considering where AD changes begin and how they spread, Hauw, Duyckaerts, Delaère and Piette (1990) comment that while it follows that if it is hypothesized that there is a regular increase in AD lesions in an identified area, then it must be accepted that the changes begin in the area in which they are the densest, such a conclusion could be a "mirage, since mild changes occurring in large areas could concentrate through anatomical pathways to small structures where they would appear very dense and could be taken as more precocious" (p. 63). They conclude that there is no consensus regarding the distribution of changes in AD but identify the main hypothetical pathways: olfactory, limbic, associative cortico-cortical, corticosubcortical or subcorticocortical. They also list other explanations: selective vulnerability of some neuronal groups; special metabolism or vascularization of some areas or of specific cell types; selective involvement of a specific system of neuromediators; high sensitivity of long axons; regional variations of amyloidogenesis or of cerebral blood vessel permeability; and the vulnerability of phylogenetically recent areas. The last explanation is developed by S. I. Rapoport.

A Phylogenic Disease

S. I. Rapoport (1990) argues that "AD is a phylogenic disease" (p. 1). Rapoport points out that AD is primarily associated with the association neocortices, and that outside the neocortex AD pathology is mainly in those brain regions which are functionally and anatomically connected with the association neocortex. Those areas are the medial septal nucleus, the nucleus basalis of Meynert, CA1 and subicular subfields of the hippocampal formation, layers II and IV of the entorhinal cortex, corticobasal nuclear group of the

amygdaloid formation, and the cortically projecting neurons of the dorsal raphe and the locus coeruleus. The author asserts that these regions are "disproportionately" evolved in higher primates, particularly in hominids and speculates that "regional vulnerability to the disease may have been introduced into the primate genome during evolution" (p. 1). S. I. Rapoport (1990) hypothesizes that the rapid evolution of higher primate brains came about by genomic changes leading to altered expression of genes coding for products in the association neocortices and their connections. Such changes may have included "regulatory mutations" leading to an altered expression of a regulatory enzyme. A regulatory mutation could have, S. I. Rapoport suggests, promoted brain accumulation of the amyloid precursor protein and the mRNA for this protein is expressed more in the association cortices than in the primary sensory or motor cortices. Some regulatory genes which are implicated in the histopathological changes in AD are linked to human chromosome 21.

Genetic Defect

S. I. Rapoport (1990) suggests that AD could have appeared following an evolutionary change in the primate genome and notes that such a change is consistent with evidence for genetic factors in the pathogenesis of AD. It has been known for some years that the brains of Down's syndrome (DS) individuals older than 40 years exhibit histopathological changes of the "same density, chemical and antigenic properties, and regional topography as do brains of AD patients" (p. 11), though St George-Hyslop et al. (1987) suggest that it is not clear that all DS individuals invariable develop a clinically apparent dementia despite the neuropathological changes. Nevertheless, the similarity of the changes in Down's syndrome, trisomy 21, suggests a genetic linkage to chromosome 21. That chromosome has been implicated in some cases of early-onset familial AD, though not in all cases of early-onset AD.

There is less genetic evidence for the involvement of chromosome 21 in late-onset AD. Pericak-Vance et al. (1988) undertook linkage studies to test the localization of both early-onset (mean age of onset <60 years of age) and late-onset (mean age of onset >60 years) on chromosome 21. They "failed to establish linkage and excluded linkage from a large portion of the region where the early onset Alzheimer's disease was localized" (p. 271), and concluded that more than one etiology exists for AD. Anderton (1988) reports

that despite the excitement generated in 1987 when it was found that the familial Alzheimer's disease (FAD) gene as well as the amyloid beta-protein gene were located on chromosome 21, other research has demonstrated that the locus of the FAD gene is not identical with the beta-protein locus (St George-Hyslop et al., 1988). St George-Hyslop et al. reported in a paper published in early 1987 that the FAD gene is located outside the DS region (21q22) and in the 21q11.2-21q21 region of chromosome 21.

Alpérovitch and Berr (1988) report that complications in genetic studies of familial AD arises from the absence of or methodological difficulties with epidemiological studies. They argue that "case-control studies have yet to provide clear evidence for familial aggregation of DAT" (p. 31). One difficulty that arises is the identification of probands. Because DAT is defined by both clinical and pathological features it is difficult, they suggest, to meet both criteria in epidemiological studies. They report that familial risk in DAT has been investigated in a "very small number of epidemiological studies" (p. 35), and list eight such studies. The frequency of DAT in relatives could be calculated in only two of the studies. One study (Breitner & Folstein, cited in Alpérovitch & Berr, 1988) found that among relatives, frequencies of cases (8.5%) was significantly greater than the frequency in controls (2.6%), while in the second (Chandra et al. cited in Alpérovitch & Berr) the frequencies did not differ (6.6% and 6.8%). Alpérovitch and Berr note, however, that in the Chandra study of the 175 cases of dementia reviewed, only 74 met the NINCDS-ADRDA Work Group (McKhann et al. 1987) and in 70 of those, onset of the dementia was after age 70. They conclude, "So far there is no strong epidemiological evidence than an increased familial risk in DAT exists" (p. 37).

Folstein, Warren and McHugh (1988) state linkage studies are further complicated by the probability of genetic heterogeneity in AD families. They suggest that three phenotypic features may show heterogeneity in AD. Those features are the cognitive syndrome, the age of onset, and the severity of dementia relative to neuropathology. Folstein et al. argue that the cognitive syndrome of amnesia, aphasia, apraxia, and agnosia (AAAA) can serve to divide AD cases into subgroups. They report, for example, that patients with aphasia may characterize a subgroups of patients with early onset of dementia and an accelerated rate of progression. Folstein, Warren and McHugh (1988) state

further that they have found that the "relatives of probands with the AAAA syndrome had a higher risk of becoming demented than did the relatives of cases with the incomplete syndrome or a normal mental state" (p. 6). They assert that cases divided by age of onset, a second aspect of phenotypic heterogeneity, differ with regard to (a) psychological features, especially language disturbance and incidence of major depression; (b) somatic features, including platelet membrane fluidity and fingerprint pattern; (c) risk to relatives; and (d) neuropathology.

The issue of severity of dementia relative to neuropathology, a third phenotypic feature, is particularly difficult. There are individuals who present with a dementia not distinguishable from AD on clinical examination who lack distinctive histologic features of AD (Knopman, Mastri, Frey, Sung, & Rustan, 1990) while other individuals demonstrate the neuropathologic features of AD with no evidence of dementia (Fitch et al., 1988; Katzman et al., 1988, cited in Folstein et al. 1988). Resolution of the problem of phenotypes will aid in the design of genetic linkage studies, Folstein et al. argue and suggest the following:

> . . . families chosen for linkage studies should have high rates of AD diagnosed by rigorous criteria, and low rates of phenocopies. These would include families with a high proportion of cases with amnesia, aphasia, apraxia, and agnosia and exclude families with possible presbyophrenia or vascular disease. Families with younger age of onset should thus be studied first since those families have higher rates of amnesia and aphasia and lower rates of simple senile dementia and stroke. Another way of improving accuracy and reducing heterogeneity of families and cases in linkage studies rests on the common-sense suggestion that we should understand one thing thoroughly before trying to divide it into two things (Folstein et al., 1988, p. 10).

Aluminum

A review of the nature of Alzheimer's disease would not be complete without addressing the question of the role of aluminum in the pathogenesis and etiology of the disease as there is no factor that is more frequently identified in the public mind with Alzheimer's disease than is aluminum. The

matter has aroused such scientific debate that the journal *Neurobiology of Aging* devoted an entire issue to the problem in 1986.

One of the seminal papers on aluminum and its relationship to Alzheimer's disease is by D. R. Crapper McLachlan (1986). Crapper McLachlan reported that by 1986 at least nine different laboratories employing four different techniques had found elevated aluminium concentrations associated with Alzheimer's disease on four continents, Australian, Europe, Japan and North America. An association was also noted between aluminum concentrations and other neurodegenerative diseases with Alzheimer type neurofibrillary degeneration. He reported, further, that there were four principal loci within the Alzheimer affected tissues that exhibited elevated concentrations of aluminum: DNA containing structures of the nucleus, protein moieties of the neurofibrillary tangle, the amyloid cores of senile plaques, and cerebral ferritin. Crapper McLachlan suggests the central question is the role aluminum may play in either the etiology or the pathogenesis of Alzheimer's disease. He indicates that there are two competing hypotheses. The first suggests that aluminum is a trivial marker of the disease that accumulates passively in neurons compromised by the disease and is not an etiological agent. The second hypothesis argues that aluminum is a pathogenic agent in the neurodegenerative processes associated with Alzheimer's disease.

While acknowledging that the evidence of the role of aluminum in the pathogenesis of Alzheimer's disease is circumstantial and that direct cause and effect observations will be difficult to obtain because "no animal species other than man undergoes an analogous neurodegenerative change" (Crapper McLachlan, 1986, p. 526), Crapper McLachlan favours the hypothesis that aluminum is an important pathogenic factor in Alzheimer's disease. He argues that the presence of aluminium in human degenerative disease indicates that the primary etiological events responsible for the initiation of the disease . . . alters either the membrane barriers or the aluminum tolerance gene permitting aluminum to accumulate in neurons. From this point of view, aluminum is not the cause of the disorder but may be an important neurotoxic factor in the pathogenesis of the degenerative process (p. 530).

Krause and Forbes (1992) summarize some of the evidence linking aluminum and Alzheimer's disease. They report that "at least seven investigations" in

different parts of the world have found significantly elevated levels of aluminum either in comparing Alzheimer's disease patients with non-demented controls or in comparing the regions of Alzheimer's disease patient's brains with extensive neurofibrillary tangles with those parts of the brains without the tangles. They acknowledge, however, that two such studies were negative. Krause and Forbes cite correlational and epidemiological studies from Norway, the British Isles, and the State of Washington showing an association between aluminum and Alzheimer's disease. A Norwegian study found a significant correlation of 0.25 between the aluminum content of drinking water in municipalities and their age-adjusted death rates with death certificates mentioning dementia. In England and Wales epidemiological studies found that the incidence of Alzheimer's disease was 1.5 times greater in districts where the aluminum concentration in drinking water exceeded 0.11mg/l than where the concentration was below 0.01mg/l. In Washington, a case-control study found a significant relationship between prior use of aluminum-containing antiperspirants and Alzheimer's disease with a ratio of 1.6. Despite their stated intention of summarizing studies that link aluminum and *Alzheimer's disease*, Krause and Forbes then briefly review studies of dialysis dementia and studies demonstrating that the injection of aluminum into the brains of rabbits and cats produce "neuropathological changes that are similar, though not identical to those in AD" (p. 98). Bradley (1990) also considers these changes in an article on theories of causation of Alzheimer's disease. While such studies yield evidence that aluminum is a neurotoxin, they contribute relatively little to establishing the role of aluminum in Alzheimer's disease.

Alfrey (1986) points out that while it is well established that aluminum is toxic to neurological, skeletal, and hematopoetic systems, its neurotoxicity is manifested in a distinctive clinical picture characterized by speech disturbance, seizures, hallucinations, and myoclonus. These clinical features typically arise only late in the course of Alzheimer's disease. Alfrey also notes that when the neurotoxicity is manifested, it is usually associated with aluminum-induced bone disease and anemia, and that the slight increase in brain aluminum found in individuals with Alzheimer's disease is much less than that required to produce dialysis encephalopathy. Further, he reports that while chelation therapy benefits individuals suffering from

dialysis encephalopathy, it does not benefit Alzheimer's patients. Alfrey points out that elevated brain aluminum levels are also found in numerous other conditions including acoustic neuroma, Huntington's disease, cerebrovascular disease, guamanian ALS, and Parkinson' disease. He concludes:

> In summary, in view of the inconsistent findings of elevated brain aluminum in Alzheimer's disease, lack of alteration of other tissue stores of aluminum, failure to find other evidence of aluminum toxicity and the clinical and anatomical dissimilarity between Alzheimer's disease and what has been reasonably well established as aluminum neurotoxicity in man, it seems unlikely that aluminum plays any role in the pathogenesis of Alzheimer's disease. It is more likely that the elevated levels of aluminum sometimes found in Alzheimer's patients are a result of rather than the cause of the damage. (Alfrey, 1986, p. 544).

Wisniewski, Moretz and Iqubal (1986) also conclude that there is no evidence that aluminum plays a role in the etiology or pathogenesis of Alzheimer's disease. They report that McDermott (cited in Wisniewski et al., 1986) using atomic absorption spectroscopy found no difference in brain aluminum concentration between SDAT patients and age-matched controls, and that Markesbury (cited in Wisniewski et al., 1986) obtained similar results using neutron activation analysis. They further report Traub (cited in Wisniewski et al., 1986) found in analysis of samples from a wide range of neurodegenerative diseases (SDAT, ALS, Guamanian-ALS, parkinsonian dementia and Creutzfeld-Jakob disease) elevated aluminum levels in some cases, but aluminum levels were neither consistently within a given disorder, nor in all the disorders. Wisniewski et al. describe important differences between Alzheimer's disease and aluminum-induced CNS changes. They point out that neurofibrillary changes occur extensively throughout the spinal cord and in specific regions of the cortex in aluminum-treated rabbits but that neurofibrillary changes are not found in the spinal cord in Alzheimer's disease patients. The association of neurofibrillary changes and neuritic plaques is found in AD but not in aluminum-treated animals. They note, further, that there is a difference in the cellular topography of neurofibrillary changes in Alzheimer's disease and aluminum-treated animals. In Alzheimer's disease the neuro-fibrillary changes occur in the nerve cell

bodies and the terminals, whereas in the aluminum-treated animals the changes occur in the perikaryon and proximal parts of axons and dendrites, but not in their distal parts and terminals. Another study (Winkleman & Ricanati cited in Wisniewski et al., 1986) demonstrated that the type of spongy changes and their distribution in dialysis encephalopathy were different than those seen in Alzheimer's disease. They conclude that there is little evidence that aluminum plays a role even as a co-factor in Alzheimer's disease.

In summary, while there are few researchers suggesting that aluminum is the primary etiological agent in Alzheimer's disease, some (Crapper McLachlan, 1986; Khachaturian, 1986; & Bradley, 1990) are prepared to consider it as a co-factor. Some (Ghetti and Bugiani, 1986; Pettegrew, 1986) see merit in further investigation of the relationship between aluminum and Alzheimer's disease. Others (Alfrey, 1986; Wisniewski et al., 1986) appear convinced that aluminum plays no significant role in the etiology or progression of Alzheimer's disease.

Amyloid ß Protein

Perhaps the most promising current research directions to date toward understanding the etiology of Alzheimer's disease is that focused on the amyloid precursor protein (APP), or more precisely on the -40-amino acid fragment of the molecule referred to variously as the amyloid ß protein (AßP, AP), A4 or ß/A4. Amyloid deposition in the brain yields abnormal fibrous protein deposits within the brains of Alzheimer's patients resulting in the senile plaques, neurofibrillary tangles, and deposits on the walls of cerebral blood vessels that are characteristic of Alzheimer's disease and the deficits in neurotransmitters, transmitter enzymes and receptors (Hardy & Allsop, 1991).

Amyloid is a generic term which describes a set of chemically heterogeneous proteins occurring in a number of tissues, neural and non-neural. The amyloid ß protein precursor is a membrane-spanning glycoprotein (Selkoe, 1990) with a long extracelluar NH_2-terminal and a short intracellular C-terminal tail. At least five alternative transcripts of the APP gene have been identified (Hardy & Allsop, 1991), the three most abundant of which are APP-695, -751, and -770. Hardy and Allsop report that in most human tissues the transcript APP-770 is the most abundant, but in the CNS, APP-695 is more

abundant. The precise role of APP is not clearly understood. Regland and Gottfries (1992) argue that "since the gene encoding APP has been well preserved during the course of evolution, it probably has some important function" (p. 467). They note that human blood platelets contain considerable amounts of APP which they release when they are activated, such as at injury sites as part of the body's blood-clotting response, and suggest that APP may act as a growth factor. Regland and Gottfries (1992) comment that a role in repair is suggested by the finding that AP (amyloid ß protein) is deposited in the brain within a few days of severe head injury. The third role of APP may be as a protease inhibitor which stops process extension and promotes stable cell-to-cell interactions. Hardy and Allsop (1991) essentially agree and indicate that the physiological functions of APP appear to include protease inhibition, a role in cell adhesion and in regulation of cell growth.

A number of researchers (Gandy & Greengard, 1992; Hardy & Allsop, 1991; Sisodia, Koo, Beyreuther, Unterbeck, & Price, 1990) agree that normal cleavage of APP occurs within the ß/A4 segment, and that cleavage within that segment does not lead to the deposition of the amyloid of senile plaques, neurofibrillary tangles or the deposits around cerebral blood vessels, that is, "an intact amyloidogenic ß/A4 fragment is not generated during normal APP catabolism" (Sisodia et al., 1990, p. 492). Gandy and Greengard (1992) assert that the major or normal "processing/secretion event in the biology of APP precludes amyloidogenesis by cleaving APP within the ß/A4 domain" (p.108). The ß/A4 fragment is the major proteinaceous component of the amyloid deposits in the brains of AD suffers and of the 'diffuse' deposits found in the brains of younger trisomy 21 individuals. The accumulating body of data suggests, according to Selkoe (1990), that the deposition of ß/A4 may play a seminal role in AD.

It appears certain that some abnormal proteolysis is responsible for the cleavage at two sites, one extracellular and one within the cell membrane, in the APP macromolecule that liberates the intact ß/A4 fragment. The mechanism by which the dual cleavage occurs is unclear, but a genetic aberration hypothesis is favoured. Such a hypothesis is suggested by mutations associated with familial cerebral amyloidoses as hereditary cerebral amyloid angiopathy of the Dutch type, familial Alzheimer's disease and with the over-expression of APP in Down syndrome. The neuropathology of ß/A4 is not well

understood. Hardy and Allsop (1991) report that synthetic ß/A4 peptides could spontaneously aggregate into amyloid fibrils, and that a ß/A4 25-35 peptide was tropic at low concentrations to undifferentiated rat hippocampal neurons but toxic at higher concentrations to mature neurons. Further research suggested that the neurotoxicity of the peptide was enhanced by nerve growth factor.

While there is compelling evidence, according to Gentleman (1992), that ß/A4 plays a role in the induction of neurofibrillary pathology, the main structural element of the mature senile plaque and neurofibrillary tangle are paired helical filaments (PHF). The precise relationship between ß/A4 and PHF and their role in neuronal loss is not understood . Hardy and Allsop (1991) report that it has been suggested that PHFs are composed of ß/A4, but argue that suggestion is highly controversial. They acknowledge that some tangles do react to ß/A4 antibodies, but point out that ultrastructural observations indicate that the finding is due to the secondary deposition of amyloid fibrils on the surface of the tangles, and argue that the most convincing data suggests that "PHFs consist, at least in part, of an abnormally phosphorated fragment of one or more isoforms of tau protein" (Hardy & Allsop, 1991, p. 385). Regarding neuronal loss, they make two important observations. First, "the affected neurons do not share any particular transmitter or any other biochemical marker tested so far" and, second, "selectivity of neuronal loss appears to be anatomically determined" with pathology spreading along neuronal pathways (p. 385). Hardy and Allsop view the progression of the disease as proceeding from altered APP metabolism resulting in amyloid deposition which leads first to the formation of neuritic plaques then to the formation of neurofibrillary tangles. Both plaques and tangles lead to neuronal damage, including the depletion of transmitters, and eventually, in Alzheimer's disease, to dementia. They state too little is known about the distribution, biochemistry and functions of APP and of neuronal networks to formulate a hypothesis of the apparent selective vulnerability of the hippocampal/amygdala complex but suggest that the disease may start in the hippocampus because it is an area in which synaptic remodelling--and presumably APP utilization--happens most frequently. An alternative explanation of the selective vulnerability of the hippocampal/amygdala complex offered by Yanker et al. (cited in Hardy & Allsop, 1991) is the neurotoxic interaction between ß/A4 and

nerve growth factor. With regard to the spread of the disease process from the hippocampus, Hardy and Allsop suggest that electrical signalling along neuronal pathways and the transfer of pathogenic molecules between neurons, perhaps through the APP transported along axons, are important factors.

Regland and Gottfries (1992) describe the process outlined above as "the primary amyloid hypothesis" and offer an alternative hypothesis. They assert that the primary amyloid hypothesis is based on two different mechanisms: overexpression as in Down's syndrome and a mutational defect as in familial Alzheimer's disease. Regland and Gottfries question whether the two separate mechanisms are compatible in a unifying hypothesis. They remind that sporadic or non-familial Alzheimer's disease accounts for the majority of Alzheimer's disease cases and suggest that overexpression or a mutational gene defect is not likely to explain all sporadic forms. They argue, further, that deposition of ß/A4 is not invariably associated with the neurofibrillary tangles characteristic of Alzheimer's disease and point out that amyloid plaques are common, and often in high density, in the cortices of cognitively normal elderly patients. Regland and Gottfries believe these observations indicate a mechanism other than amyloid deposition must account for Alzheimer type dementia. They argue that rather than being a factor in the etiology in Alzheimer's disease, ß/A4 is an endogenous protective reactant activated by injury to brain cells, and that it is important in the survival of cells. Regland and Gottfries (1992) comment:

> The formation of plaque amyloid is to be considered a non-specific response of the neuronal network to different kinds of injury to the brain tissue, and the distinction between normal brain ageing and AD is quantitative rather than qualitative. Most human beings and lower primates acquire some AP deposits during ageing, but this process is accompanied by little neuronal alteration or mental dysfunction, because the *AP deposition is not the central event in the pathogenesis of sporadic Alzheimer's* [italics added]. The disease is most likely to develop when APP is insufficient whether because of a genetic defect or because of intense exposure to causal factors in the environment (p. 468).

Regland and Gottfries (1992) acknowledge that if their view is correct, the apparent relationship between Alzheimer-type changes and Down's syndrome would be "puzzling" since the overexpression of the gene and the more APP resulting should be protective. They conjecture that "perhaps only the stress-induced APP is both protective and amyloidogenic, whereas the constitutively expressed APP is not protective but toxic, if present in high concentration" (p. 468).

While Regland and Gottfries's alternative hypothesis is intriguing, it lacks parsimony, and it is not clear that the "primary amyloid hypothesis" cannot deal with both the tropic effect of APP and the neurotoxic effect of ß/A4.

The amyloid hypothesis is appealing for, like the cholinergic hypothesis, a mode of treatment or modes of treatments are implicit in the hypothesis: prevent the missense cleavage that yields the problematic ß/A4 fragment; bind the fragment such that it is innocuous; find/develop a protease that will cleave the fragment; and so on. The hypothesis is appealing as well because it is compatible with and may well provide the medium in which to bind many of the hypotheses and observations reviewed in this section. Unfortunately, the current research does not promise a cure in any definable future.

Perhaps the status of research into the etiology of Alzheimer's disease is best summed by Gene Cohen (1988):

> Theories of what causes Alzheimer's disease have not been lacking. Clues are myriad and mounting. But the solution as to its etiology is still elusive. It is in the nature of how we look for problems as well as solutions that we seek the starting *point*, the single critical event. In much of life and disease this seemingly reductionistic approach often pays off . . . .
>
> But sometimes in life and medicine the single causative factor cannot explain everything. The genetic evidence suggests more than one subtype of Alzheimer's disease; the findings from studies of Creutzfeldt-Jakob disease show how two factors (genetics and a virus) can interact to cause a degenerative brain disorder resembling Alzheimer's disease; clinical courses of varying durations among those afflicted with Alzheimer's disease may also suggest the role of multiple

factors effecting this variability. With all of this said and summarized, the origin of Alzheimer's disease remains a mystery (Cohen, 1988, pp. 137-138).

AN ADDENDUM

Since the above review was completed, exciting new research has shown a strong link between apolipoprotein E (apoE) and Alzheimer's disease (Poirier, Davigonon, Bouthillier, Kogan, Bertrand & Gauthier, 1993; Saunders, Schmader, Breitner, Benson, Brown, Goldfarb, Goldgaber, Manwaring, Szymanski, McCown, Dole, Schmechel, Strittmatter, Pericak-Vance & Roses, 1993). Poirier et al. (1993) describe apoE:

> Apolipoprotein E (apoE) is a polymorphic protein associated with plasma lipoprotein. It interacts with the 'remnant receptor' (apoE receptor) and the low-density-lipoprotein (LDL) receptor (apoE/B receptor) of the liver and other organs to modulate the catabolism of triglyceride-rich lipoprotein particles. ApoE is unique among apolipoproteins in that it has a special relevance to nervous tissue. It is involved in the mobilisation and redistribution of cholesterol in repair, growth, and maintenance of myelin and neuronal membranes during development or after injury (Poirier et al. 1993, p. 697).

ApoE is present in the plaques and dystrophic neurites that are pathogonomic of AD, and apoEmRNA has a role in compensatory central-nervous-system sprouting and synaptogenesis which are reduced in the hippocampus in AD suffers (Poirier et al., 1993). Poirier et al. explain that "ApoE is encoded by a gene on the long arm of chromosome 19, within a region previously associated with familial late-onset AD. Common polymorphisms are determined by alleles designated ε4, ε3, and ε2" (p. 697). Six common apoE polymorphisms arise as a result: E2/2, E3/3, and E4/4 (in homozygotes) and E3/2, E4/2, and E4/3 (in heterozygotes). Lipoproteins associated with apoE4 are, by their report, "cleared more efficiently than the ones containing apoE3 and apoE2" (p. 697). The efficient clearing of lipoproteins associated with apoE4 may alter, they suggest, brain reinnervation processes which depend on those lipoproteins, and they note that sporadic AD patients, relative to normal controls, have unusually high plasma levels of lipoprotein-cholesterol and poor reinnervation capacities.

Persons at greatest risk for AD are those with the homozygote E4/4 and the heterozygote E4/3. Poirier et al. report that in a pool of 418 octogenarians, 83% of those with the homozygote E4/4, were diagnosed with AD, and note that the ratio is similar to the 91% found for familial cases. They also find evidence for early- and late-onset forms of AD. Poirier et al. found two peaks for ε4 prevalence, one at 55-65 years, and a second at 75-85 years. Among octogenarians, there is increased prevalence of E4/3 but not E4/4. They speculate that persons with the homozygote E4/4 are selected against by the high risk of arteriosclerosis that accompanies the E4/4 form.

Saunders et. al. (1993) demonstrated that individuals with amyloid forming diseases, familial Creutzfeldt-Jacob disease, familial amyloidotic polyneuropathy, and Down's syndrome, do not have a ε4 frequency that is significantly greater than that of normal controls. In their study, only individuals with probable or possible AD showed a significant difference from controls and that difference was strikingly significant ($p < .00001$). They conclude that "the relevant genetic factor in late-onset AD is the allele determining apoE type 4" (p. 710).

Poirier et al. (1993) suggest an association of apoE and βA4 amyloid in AD.

> ApoE can interact directly with βA4 amyloid to form a stable adduct and it is also found in senile plaques and neurofibrillary tangles. This co-localisation of apoE with the major neuropathological features of AD plus the enrichment of the ε4 allele suggest some relationship to the cause of AD. One possibility is that the age-related decline in cell number and lipid content that happens normally in the human brain is exacerbated by the presence of the ε4 allele(s) in susceptible individuals. Furthermore, if apoE disrupts lipase activity in the brain and alters the transport of cholesterol and phospholipids in brain areas vulnerable to ageing, a direct consequence would be aberrant and/or defective reinnervation and poor synaptic plasticity. (p. 699).

The apoE research is particularly promising. It provides a mechanism for both the association of βA4 amyloid with AD and the dissociation of that protein from other amyloidogenic diseases. Further, it demonstrates that

sporadic and familial AD are in all probability the same disease, and, at the same time, provides evidence for early- and late-onset forms of the disease. Finally, the apoE research suggests that treatment and, perhaps, prevention of AD are on the horizon, a distant horizon, but a perceptible one.

CHAPTER SUMMARY

Studies reviewed demonstrate that Alzheimer's disease is a major health concern that demands as much as $88 billion from the North American economy and which will affect, depending on the estimates of prevalence selected, nearly four million people on this continent by the turn of the century. While the issue is still controversial, the weight of research appears to suggest that the neuropathological changes pathognomonic of Alzheimer's disease begin in the hippocampus and spread to cortical areas. Approaches to treatment of Alzheimer's disease based on the cholinergic hypothesis have been found unsuccessful. The evidence that aluminum plays an etiological role in Alzheimer's disease is not well supported, and compelling arguments are raised against aluminum in the pathogenesis of the disorder. The most promising research in the search for the etiology of Alzheimer's disease appears to lie in the genetics of the βA/4 amyloid protein and the apo4 apolipoprotein. The apo4 research is especially interesting as it appears to suggest an outline for the resolution of a number of neurophysiological and neuropsychological questions about Alzheimer's disease, i.e., sporadic and familial AD and early- and late-onset questions. The heterogeneous presentation of AD and poor understanding of its etiology contribute to the difficulty in the differential diagnosis of AD, and it is to problems of differential diagnosis that this review now turns.

CHAPTER 3
REVIEW OF THE LITERATURE--DIAGNOSIS AND CHARACTERISTICS OF ALZHEIMER'S DISEASE

DIAGNOSIS OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a dementing disorder. That simple statement reflects the essential difficulty in the diagnosis of the disease. Hauw, Duyckaerts, Delaère and Piette (1990) point out ". . .'dementia' is a clinical term (and cannot be diagnosed with certainty by the pathologist) and 'AD' is a pathological one (conversely, it cannot be diagnosed with certainty by the clinician)" (p.55). A certain diagnosis of Alzheimer's disease requires histopathological evidence, but dementia is not diagnosable on that same evidence. Dementia requires a clinical diagnosis. While it is possible through brain biopsy to obtain histopathological evidence on demented patients in life, and such has been done (Neary et al., 1986), it is rare that such procedures are ethically justifiable. For most patients, a presumptive diagnosis of Alzheimer's disease is made on the basis of the clinical presentation. Unfortunately, the correspondence between the presumptive clinical diagnosis and histopathological evidence of AD has been less than satisfactory. Studies of the accuracy range from rates of 55% (Muller & Schwartz, cited in Wade et al., 1987) to 86% (Tierney et al., 1988), and in straight forward cases, that is, in the absence of other disease or focal neurological findings and with insidious onset of a progressive dementing disorder, 90% (Terry & Katzman, 1983).

There are a number of factors that contribute to the difficulty of clinical diagnosis of AD. The contribution of etiological uncertainty to diagnosis of Alzheimer's disease has already been discussed. While knowledge of etiology would undoubtedly assist the clinician, at the state of present knowledge, the difficulties that he or she faces in the accurate differential diagnosis of Alzheimer's disease arise elsewhere.

Alzheimer's disease is more heterogeneous in its presentation than was previously suspected. Presentation varies with stage or degree of progression, or some would argue, with subtype. Other disorders, especially cerebrovascular disorders without acute onset and other slowly progressive

dementias, confound diagnosis. And, there is not unanimous agreement on the histopathological criteria for the diagnosis of AD (Hauw et al., 1990; Tierney et al., 1988). However, it has been the absence of criteria for the clinical diagnosis that was most problematic. Steps were taken to rectify that difficulty through the establishment of a Work Group on the Diagnosis of Alzheimer's Disease through the auspices of the National Institute of Neurological and Communicative Disorders (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) to refine the clinical diagnostic criteria for AD.

The NINCDS-ADRDA Work Group: Clinical Criteria for the Diagnosis of Alzheimer's Disease

The NINCDS-ADRDA Work Group drew its representatives from professional societies and associations in psychology, psychiatry, neurology, and geriatrics. The report of the Work Group (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984) describes criteria to serve as the clinical basis for the diagnosis of AD. In presenting the report, the authors cautioned that the criteria were not fully operational because of insufficient knowledge of the disease and that the criteria must be considered tentative and subject to change. The NINCDS-ADRDA Work Group established clinical criteria for probable, possible and definite Alzheimer's disease. The description of criteria that follows is taken from *Table 1. Criteria for clinical diagnosis of Alzheimer's disease* (p. 940) in the Work Group's report.

The criteria for *definite* Alzheimer's disease are the clinical criteria for probable AD and histopathological evidence obtained from biopsy or autopsy.

The criteria for *possible* AD are a dementia syndrome in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and the presence of variations in onset, in presentation, or clinical course. Possible AD may be diagnosed in the presence of a second systemic or brain disorder sufficient to produce dementia, but which is not considered to be the cause of the dementia. The report states that this designation should be used in research when "a single, gradually progressive

severe cognitive deficit is identified in the absence of other identifiable cause" (p. 940).

The clinical criteria for *probable* AD are the most extensive and include descriptions of features that must be included for diagnosis, that support a diagnosis, and that are consistent with a diagnosis of probable AD. Criteria that make a diagnosis of probable AD unlikely or uncertain are also included. The criteria that *must be included* for a diagnosis of probable AD are dementia established by clinical examination, documented by a screening instrument, and confirmed by neuropsychological tests. The above must establish all of the following: deficits in two or more areas of cognition; progressive worsening of memory and other cognitive functions; no disturbance of consciousness; onset between ages 40 and 90; and the absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition. Features that *support* a diagnosis of probable AD are progressive deterioration of specific cognitive functions including language, motor skills, and perception; impaired activities of daily living and altered patterns of behaviour; a family history of similar disorders, particularly if confirmed neuropathologically; normal laboratory results for lumbar puncture; normal pattern or nonspecific changes in EEG; and CT evidence of cerebral atrophy with progression documented by serial observation. Clinical features *consistent with* probable AD are, when other causes of dementia are excluded, plateaus in the course of the progression of the illness; associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss; other neurologic abnormalities including motor abnormalities with advanced disease; seizures with advanced disease; and CT normal for age.

The features that make a diagnosis of probable AD *uncertain or unlikely* include sudden, apoplectic onset; focal neurological findings, including incoordination early in the course of the illness; and seizures or gait disturbances at the onset or very early in the course of the disease.

The medical history is to be taken from the patient and an informant who is well acquainted with the patient. The medical history will begin to establish the presence or absence of other medical conditions that may

contribute to or confound a diagnosis of dementia. It will as well establish a deteriorating course and describe the tasks the patient can no longer perform adequately. Clinical examination, especially mental status examination will assess specific abilities, including orientation, registration, attention, calculation, short-term recall, naming, repetition, reading, writing and visuo-constructive (drawing, usually) abilities, as well as the patient's affective state. Particular attention should be given to depressive symptomology and the presence of delusions and/or hallucinations. The Work Group (McKhann et al., 1984) suggests "quantitative aids" to the clinical examination. Those aids include Mini-Mental State Examination, the Blessed Dementia Scale, the Hamilton Depression Scale, the Present State Examination, and the Hachinski Scale. The clinical examination includes a neurological examination sufficient to exclude neurological disorders. For purposes of neuropsychological assessment, individuals scoring in the lowest fifth percentile of their comparison group may be designated as "abnormal", and one or more abnormal scores will identify a patient who is "highly likely" to be cognitively impaired. Laboratory assessments serve primarily to enhance diagnostic accuracy by identifying other causes of a dementia syndrome though some, computerized tomography, regional cerebral blood flow, positron emission tomography, and magnetic resonance imaging, yield evidence of cerebral changes associated with a primary degenerative disorder as well as other cerebral disorders.

NINCDS-ADRDA Work Group: Histopathological Criteria

The initial report of the NINCDS-ADRDA Work Group (McKhann et al., 1984) provided the clinical criteria for the diagnosis of possible and probable AD; however, the clinical diagnosis of *definite* AD requires that all the clinical criteria for probable AD be met and that there be histopathological evidence of AD obtained through biopsy or autopsy. A second report of the Work Group (Tierney, Fisher, Zorzitto, Snow, Reid & Nieuwstraten, 1988) observes that the latter neuropathologic confirmation "presupposes the existence of morphologic criteria which are consistently applied by all pathologists" (p. 360). Herein lies a problem.

Tierney and the co-members of the Work Group point out that there are at least three positions on the morphologic criteria necessary for the neuropathological diagnosis of "pure AD". The three positions arise in regard to the brain-sites in which senile plaques (SP) and neurofibrillary tangles (NFT), the pathognomonic lesions of AD, must be found. The first position holds that AD is confirmed with the existence of SP and NFT in the hippocampus. The second requires that SP and NFT be present in the neocortex, while the third position requires that the lesions be present in both the hippocampus and neocortex. The Work Group cautions that the different criteria may lead to different conclusions on the presence of AD in the same individual.

A further difficulty arises with the neuropathological criteria in exclusion of other diseases, especially with regard to the exclusion of cerebro-vascular disease. The Work Group observes that there is considerable disagreement in the literature as to the type and extent of vascular disease in the brain required to produce dementia. That disagreement leads to variations in the exclusion criteria for definite AD. The vascular exclusion criteria vary according to both the site and the extent of vascular lesions in the brain. At least two vascular criteria have been used with regard to size: one excludes vascular lesions entirely; the other excludes only those vascular lesions that are greater than 50 ml. There are as well two different criteria for the site of vascular lesions. The first excludes lesions at any site while the second excludes only those cases with lesions in the hippocampus or the neocortex. It appears, then, that there is considerable variation in the neuropathologic diagnostic criteria for "definite" AD.

The specific objective of the study undertaken by the Work Group (Tierney et al., 1988) was to "examine the clinicopathologic relationship between the Work Group criteria for the diagnosis of probable AD and the differing sets of neuropathologic criteria for pure AD" (p.361). They studied 57 autopsied cases of which 22 cases had been diagnosed as probable AD through "rigorous adherence" to the Work Group criteria and 35 cases classified as not probable AD on the basis of those criteria. They compared those cases on each of three neuropathologic inclusion criteria and three neuropathologic exclusion criteria. (They used only three vascular exclusion criteria as there were no cases in which the vascular lesions totalled more than 50 ml.)

Their results showed that overall accuracy for each of the nine combinations ranged from 81% to 88%.

Sensitivity values ranged from 64% to 86%. When the criteria applied were one or more NFT and one or more neuritic plaques (PL) per X25 microscopic field in both the neocortex and the hippocampus or one or more NFT and one or more PL per X25 microscopic field in the neocortex, irrespective of hippocampal findings and, with both, the exclusion of any ischemic lesion irrespective of size or site the sensitivity was a low 64%. When the inclusion criteria were one or more NFT and one or more PL per X25 microscopic field in the hippocampus, irrespective of neocortical findings and the exclusion criteria were one or more ischemic lesions that totalled 50 ml or more of brain tissue in the neocortex, subcortical white matter, and/or hippocampus the sensitivity rose to 86%. They found that the greater variability in sensitivity arose in the vascular exclusion criteria applied.

Specificity, selection of those cases diagnosed as not probable AD and which did not receive a neuropathological classification as pure AD, ranged from 89% to 91% with little variability across the nine neuropathological criteria. The combination of inclusion and exclusion criteria that produced the greatest overall agreement (88%) between clinical and neuropathologic classification was, as inclusion criteria, one or more NFT and one or more PL per X25 microscopic field in the hippocampus and, as exclusion criteria, one or more ischemic lesions that totalled 50 ml or more of brain tissue in the neocortex, subcortical white matter, and/or hippocampus. (See also Hauw et al., 1990, cited earlier for a detailed examination of the topography of lesions in AD.)

The results of the Work Group's (Tierney et al., 1988) study on clinicalpathological agreement demonstrates a high degree of accuracy for clinical diagnosis when consistent criteria are applied for both clinical examination and neuropathologic classification. However, in one case examined from a selection of eight, an individual who showed significant memory impairment over a 12 month period had "no significant pathology" on any of the nine neuropathologic criteria, and two others with composite memory scores 2 standard deviations below the mean of a normal control group were classified as AD on only three of the nine neuropathologic criteria and "no significant pathology" on the other six. Knopman, Mastri, Frey, Sung and

Rustan (1990) identified another group of demented patients without the pathognomonic changes associated with AD. They labelled the disorder 'dementia lacking distinctive histology' (DLDH) and reported that it occurred as frequently as did Pick's disease in their sample. If there are individuals with dementias that are indistinguishable from AD on clinical examination, it seems appropriate to ask "Are there individual's who show, histo-pathologically, the pathognomonic characteristics of Alzheimer's disease in the absence of a clinically significant dementia?" Clearly there are such individuals. Crystal et. al (1988) followed 28 longitudinally evaluated elderly subjects with senile plagues and neurofibrillary tangle counts from standardized sections in postmortem pathology indicative of AD, yet nine of those subjects were not demented when evaluated just prior to their deaths. A few other researchers including Blessed, Thomlinson, and Roth, 1968, and Bowen, 1981 (cited in Bartus, Dean, Pontecorvo & Flicker, 1985) have also addressed the question, but a more complete answer may be necessary before the acceptability of a 12% overall discrepancy between clinical and pathological findings can be fully evaluated. It is, nevertheless, the impact of dementia on an individual in life that is, in the absence of effective therapies specific to AD or AD-like diseases, of greatest concern to the individual, to her or his family, and to health care institutions; thus, for the present, the greater need is for accurate clinical diagnosis of probable AD.

To avoid confusion of terms, a convention suggested by Leonard Berg (1988) will be followed throughout the balance of this proposal except where authors cited have used other designations. The term SDAT (senile dementia of the Alzheimer type) or DAT (dementia of the Alzheimer type) will refer to the disorder when diagnosed by clinical and laboratory criteria without histological confirmation of the disease. SDAT and DAT will be analogous to "probable Alzheimer's disease" as specified by the NINCDS-ADRDA Work Group (McKhann et al., 1984). AD will refer to the disorder diagnosed on the basis of both clinical dementia and the neuropathological changes determined by biopsy or autopsy pathogonomic of Alzheimer's disease.

LABORATORY INVESTIGATION

Modern laboratory techniques, electrophysiology (EEG), positron emission tomography (PET), single positron emission computed tomography (SPECT),

regional cerebral blood flow (rCBF), may demonstrate changes in brain physiology while computerized tomography (CT) and magnetic resonance imaging (MRI) may demonstrate structural changes in the brain that will assist the clinician in the diagnosis of AD. Laboratory examination of body fluids has been used primarily to exclude other disorders, and biopsy of neural tissue can be examined for the presence of NFT and PL. Neurotransmitters in neural tissue can also be analyzed, but as has been observed, clinicians can justify brain biopsy in only a relatively few cases. More recently, a number of papers (Farlow, Ghetti et al., 1992; Palmert et al., 1992; Van Nostrand, Wagner, Haan, Bakker, & Roos, 1992) have appeared suggesting that analysis of CSF for the level of amyloid beta-protein precursor (APP, ßAPP) may offer a less invasive procedure that will yield a reliable diagnosis of AD. And the most recent research into apolipoprotiens especially apoE 4 promises an even more reliable diagnosis.

Current research demonstrates that APP levels in CSF obtained through lumbar puncture in AD patients were 3.0 to 3.5 times lower than those in normal controls; however, concentrations of various APP derivatives (full length precursors truncated at their carboxyl-termini to produce ~25 kDa, ~105 kDa, and ~125 kDa derivatives) complicate the picture. CSF from 24 AD patients, 10 from autopsy and 14 from living patients, was analyzed and compared with Mini-Mental State testing (Palmert et al., 1990). As dementia became more severe, the percentage of the ~25 kDa form rose from 25% in patients with MMSE scores of 17 to 24, to 42% in patients with a score of 11 to 16, and to 70% in patients with a score of 0. Conversely, they report, the percentage of the ~105 kDa decreased from 65% in patients with MMSE scores between 17 and 24 to 45% in patients with a score of 11 to 16, and to 23% in patients with a score of 0. When AD patients and age-matched controls were compared, the levels of all the APP forms were significantly different but overlapping with respect to the absolute and relative levels of ßAPP. For example, the total ßAPP found in the CSF of AD cases 52-73 years was 15.9 ± 4.3 while the total for an age-matched sample was 19.3 ± 4.6. Palmert et al. (1990) comment

> These measurements cannot, therefore, be used to diagnose AD in every patient although they may be useful (1) as part of a series of tests aimed at diagnosing AD, (2) in predicting the course of AD particularly

when serial measurements are made, and (3) in monitoring therapeutic strategies aimed at reducing amyloid deposition. In addition, it is possible that an AD-like profile for these variables (increased % ~25 kDa and decreased % ~105 kDa, as was observed in the moderately and severely demented AD patients, or high absolute levels of βAPP, as was observed in the least demented AD patients), is a significant risk factor, and that a high percentage of the nondemented individuals who show such a profile will eventually develop AD (p. 1032).

Imaging

Discussion of investigation of brain physiology necessarily overlaps discussion of brain imaging. The term 'imaging' includes techniques of visually displaying both brain physiology--electrical activity, blood flow, oxygen metabolism, glucose metabolism and other activities--and brain structure. Brain electrical activity mapping (BEAM) provides a visual representation of brain electrical activity. Cerebral blood flow (CBF) measures mated with computerized tomography yields a "picture" of cerebral blood flow. PET and SPECT display brain metabolism. All these procedures provide an image of some aspect of brain physiology. Computerized axial tomography (CAT), more frequently simply called computerized tomography (CT), and nuclear magnetic imaging (NMI) or magnetic resonance imaging (MRI)--which avoids the negative connotations of the word 'nuclear'--yield images of brain structure. In the following pages discussion of investigation of brain physiology in diagnosis of AD and adjunct brain physiology imaging is followed by discussion of imaging of brain structure in AD research.

Electrophysiologic Investigations

Electrophysiologic investigations show, in general, diffuse slow-wave activity in the brains of AD patients. Liston (1979) reports, for example, that in a study of 50 DAT patients, 48 of whom underwent electrophysiologic examination, 33 or 69% showed EEG abnormalities. Of those, 31 or 94% showed diffuse slowing. Terry and Katzman (1983) assert that symmetrical, usually diffuse slowing, is one of the most consistent correlates of progressive AD changes. Electrophysiologic research has demonstrated that while the latency of P-300 is increased with age, there is a 50% to 80% increase in latency for

AD patients as compared with normal controls (Tierney et al., 1988). Blackwood, St. Clair, Blackburn, and Tyrer (1987) report decreased amplitude of P-300 as well as increased latency in DAT, but they caution that such changes are not confined to DAT, and that they occur in other dementias, mental handicap, and in normal aging. Blackwood et al. note, however, that while the changes in P-300 are similar to those found in normal aging, they are more pronounced in DAT. Albert, Duffy, and McAnulty (1990) have used brain electrical activity mapping (BEAM) to demonstrate more focal changes in two groups of DAT patients. Using the Mattis Dementia Rating Scale (DRS) and Figure 2 from the Wechsler Memory Scale, they divided 26 patients into two groups: Group 1, nine patients with a "significant and profound memory deficit", and Group 2, seven patients with "gradually progressive spatial impairment". They found significant differences between the two groups with the differences arising, primarily, in parietal regions. While Albert et al. have interpreted the results as physiologic differences between the left and right hemispheres as reflecting general memory ability and spatial ability, it seems as probable, given the nature of the instrument selected for categorization, the results reflect the differences between *verbal* memory and spatial function as the DRS memory subtests are primarily demanding of verbal memory. In any case, their results appear to suggest that there is some role for electrophysiologic examination, and BEAM in particular, in identifying more focal impairments associated with AD.

Regional Cerebral Blood Flow

Regional cerebral blood flow (rCBF) is another laboratory technique for investigating changes in brain physiology associated with AD. Measurement of cerebral blood flow involves perfusing the brain with xenon-133 or sodium pertechnetate (^{99m}Tc), stable radioactive tracers, either through intracarotid injection or, with xenon-133, inhalation. Blood flow is measured with a gamma camera, scintillation detector, or with one of these coupled with PET or CT. A number of variables may be measured: median transit time, flow through fast clearing tissue (mainly gray matter), flow through slow clearing tissue (mainly white matter), proportion of tissue clearing at a fast rate, and flow slopes as well as others. Further, measures may be taken of various brain

regions: hemispheric, cortical, subcortical, frontal, posterior, and so on. Research findings appear to suggest that the value of measurement of rCBF is equivocal.

Hunter et al. (1989) found in comparing DAT and Korsakoff's Psychosis (KOR) that in DAT there was a marked and consistent *trend* for cognitive scores to be inversely associated with median vascular transit time. However, Liston and La Rue (1983b) suggest after reviewing a number of studies that it would be difficult to categorize individuals as DAT or MID on the basis of CBF. Hachinski (1978) found a significant decrease in the proportion of tissue which cleared at a fast rate (*Wf*) in both MID and DAT groups as compared with controls, and a significant reduction of mean hemispheric flow on all variables except flow through slow clearing, mainly white, tissue for the MID group. His results further showed a positive correlation between mean hemispheric flow and the Information Score of the Information-Memory-Concentration Test (Blessed, Tomlinson, & Roth, cited in Hachinski, 1978) for the MID groups but no such relationship for the DAT sample.

In a somewhat different experiment, Judd et al. (1986) were able to use CBF techniques to demonstrate a correlations between cognitive measures and vasomotor responsiveness in response to 100% oxygen in patients with MID but not in patients with AD or neurologically normal individuals. Papers by Gustafson and Nilsson (1982) and Hagberg and Gustafson (1985) on differential diagnosis of dementia both include rCBF among the clinical measures taken among their subjects, but both papers fail to comment further on the precise measures made or the results of those measures among the patient groups examined (AD, Pick's Disease, and MID). Hagberg and Gustafson comment in concluding their 1985 paper that the relevance of the clinical rating scales they developed supported by a good correspondence between the clinical diagnosis and the rCBF findings without description of the rCBF characteristics of the groups examined.

Kobari, Meyer, and Ichijo (1990) included local cerebral blood flow (LCBF) measures in examining the relationship between leuko-araiosis in normal volunteers, MID patients, and DAT patients. They found that while overall LCBF values were reduced among subjects with leuko-araiosis, LCBF differences reached significance only for subcortical gray matter alone and for cortical

and subcortical gray matter alone. The differences in local lambda values (local partition coefficients for xenon gas) between groups with and without leuko-araiosis were not significant. And, while it is noted that the frequency of leuko-araiosis between DAT and MID patients was not significant, LCBF values for those groups are not provided.

In sum, the literature does not suggest that measurement of CBF values makes a unique contribution in the diagnosis of AD.

Positron Emission Tomography

Positron emission tomography yields high resolution images reflecting differences in metabolism in cortical and subcortical brain regions. The process requires the injection of the radioactive isotope fluorine-18 as 2-fluoro-2-deoxy-D-glucose to measure glucose metabolism. Local cerebral metabolic rates for glucose (LCMR) and/or regional cerebral metabolic rates for glucose (rCMRglc) are obtained. A number of PET studies (Chase et al., 1984; Haxby, 1990; Martin et al., 1986; McGeer et al. 1990) have demonstrated significant reduction of cerebral glucose metabolism in the association cortices of AD suffers relative to normal controls. The parietal and posterior temporal areas tend to show the greatest changes in the early stages of DAT. The primary areas--sensorimotor, visual and auditory cortices--are relatively spared as are some subcortical structures, namely, the thalamus, caudate and lenticular nuclei. The cerebellum is also spared. The studies listed above also demonstrate positive relationships between glucose utilization and cognitive performance and between metabolic asymmetries and cognitive asymmetries. In general, DAT patients showing relatively greater language/verbal deficits have reduced left-hemisphere glucose metabolism while patients with relatively greater visual-spatial deficits show reduced right-hemisphere glucose metabolism.

While PET appears a useful tool in diagnosis and charting the progress of DAT, it does have limitations in early diagnosis. Haxby (1990) reports on the basis of a number of PET studies that asymmetrical changes in hemispheric metabolism correlate with asymmetrical verbal and visual spatial abilities for individuals with moderate impairment; however, in patients with mild DAT, he found metabolic asymmetries before the patients demonstrated any significant

impairment on *nonmemory* [italics added] neuro-psychological functions. Despite the absence of impairment at initial assessment, at a mean follow-up period of 24 months the patients had developed significant impairments of nonmemory visual spatial and language abilities, and the impairments were in the directions that would be expected on the basis of the metabolic asymmetries. While these findings appear promising, Haxby cautions that it is important to emphasize that abnormal rCMRglc have not been demonstrated in the "preclinical stages of DAT" (p.117), that is, before the impairment of memory; hence, memory impairment precedes neocortical metabolic changes in DAT observable on PET scan. If memory impairment in DAT precedes those metabolic changes detectable through PET scan and early diagnosis is essential, the value of PET as a tool of initial diagnosis or very early diagnosis may be limited.

Single Positron Emission Computerized Tomography (SPECT)

Separation of SPECT, PET and RCBF or LCBF is somewhat arbitrary as SPECT and PET studies frequently involve and reflect studies of cerebral blood flow. The separation here reflects, for the most part, the researcher's title rather than a substantive difference in content. The studies reviewed here all involve cerebral blood flow imaged using SPECT techniques, but in each case the authors have given SPECT priority in their titles.

As with PET, a number of tracers can be used in SPECT studies: ^{133} Xenon in oxygen, ^{123}I in N-iso-propyl-p-iodamphetamine, ^{99m}Tc in hexamethyl-propyleneamine oxime (HMPAO), and others. While SPECT does not yield the quality of images obtained through PET, it is less expensive and requires a less highly trained technical staff. In general, SPECT studies of AD yield results similar to those obtained with PET; they show defects in metabolism in temporal and parietal lobes. SPECT studies parallel those done with PET. For example, a study by Burns, Philpot, Costa, Ell, and Levy (1989) of the relationship of ^{99m}Tc-HMPAO and a number of clinical and neuropsychological characteristics found significant correlations between posterior parietal lobe activity and apraxia, temporal lobe activity and memory loss, and left frontal, left lateral temporal, and left posterior parietal lobe activity and language dysfunction.

Unlike some other studies, the study by Burns et al. (1989) did find significantly lower metabolic activity bilaterally in the temporal and posterior parietal lobes of AD patients than in normal controls. However, another study by Waldemar, Paulson, and Lassen (1990) using [^{99m}Tc]HMPAO obtained less definitive results, and they dispute the claim by Burns et al. and others that SPECT studies have demonstrated that bilaterally reduced uptake in the posterior temporoparietal regions is a distinctive feature of AD sufficient to differentiate it from MID. Waldemar et al. indicate that their research yielded variable results such that AD could not be confidently distinguished from MID or certain frontal dementias on the basis of SPECT. A study by Bonte, Ross, Chehabi and Devous (1986) coupling RCBF and SPECT yielded similar results, i.e, DAT patients are significantly different than healthy controls for some areas, but large variance in patient results, and a lower but nonsignificant difference for whole brain mean flow between controls and patients minimize the clinical utility of the findings.

Jagust, Reed, Seab, and Budinger (1990) used the blood flow tracer [^{123}I]*N*-isopropyl-p-iodoamphetamine to examine whether presenile-onset patients differed from senile-onset patients on clinical and neuropsychological variables, and whether the differences found were associated with differences in rCBF. Unfortunately, their presenile-onset group was significantly more impaired than their senile-onset group, raising possibility that neuropsychological and rCBF results reflected level of impairment rather than presenile- or senile-onset. The presenile-onset groups showed significantly lower rCBF ratios in left-frontal regions relative to right, and a significantly lower average of all rCBF ratios, but those results are compromised by the significantly greater impairment of the early-onset group. When the patients were re-grouped into mild to moderate impairment group (MMSE scores greater than 15) and a severe impairment group (MMSE scores less than 15), the average rCBF ratios were significantly lower in the more severely demented group. Jagust et al. (1990) conclude that the results of their SPECT study "appear" to demonstrate a functional impairment of the left frontal cortex in the presenile group that is not simply related to level of impairment. They comment, "Findings from this study provide evidence for a previously hypothesized relative accentuation of the disease process in the

left hemisphere of patients with the early onset of dementia symptoms" (p. 632).

In contrast, Burns et al. (1989) report that right/left asymmetries have been found in AD patients using both PET and SPECT and assert "It has been found that late onset AD is associated with deficits of the left side whereas early onset AD is associated with deficits on the right" (p. 252). The comments by the two groups of researchers appear diametrically opposed, and while it is likely that some differences in research results might be resolved on the basis of methodological differences, it seems appropriate to observe that SPECT does not offer, at present, a diagnostic tool of primary importance in clinical practice.

In commenting on PET and dementia, Benson (1988) observes that while numerous studies agree that focal hypometabolism affecting the parietal-temporal regions is demonstrable in early DAT, the degree of hypometabolism is "not great" and that it demands sophisticated instrumentation for detection. Worse, from a diagnostic point of view, the changes noted do not appear specific for DAT. He comments, "The early claims for PET as a major clinical tool for the detection of DAT remain unfounded and PET appears to have a limited future as a diagnostic technique in dementia" (p. 87). The same observations would appear to apply equally as well to SPECT.

Imaging Cerebral Structure

Imaging of cerebral structure in clinical investigation of DAT serves primarily to exclude other causes of dementia. George et al. (1990) report that while a number of studies have demonstrated correlations between generalized ventricular and sulcal enlargement and the presence and severity of AD, the correlations are weak and the extent of the changes overlap those observed in normal aging.

Neuroimaging data collected by George and his colleagues suggest stronger correlations between ventricular dilation and measures of AD when measures of ventricular volume are taken from slices below the pineal level, and that CT data most relevant to AD changes are obtained in the basal temporal lobe especially in the enlargement of the choroid and hippocampal fissures. Acting on that observation, George et al. (1990) implemented a CT protocol designed to optimally visualize changes in the temporal lobes. Key

to the visualization of the basal temporal lobe was a series of 5-mm cuts with the scanning plane oriented 20 degrees negative to the canthomeatal line obtaining sections parallel to the long axis of the temporal lobes. With that scanning orientation, the temporal horns, the medial temporal cortex, and the lateral temporal cortex were visualized simultaneously on at least one and often two or three slices.

Scans were evaluated on five variables: temporal horn enlargement; medial cortical atrophy; lateral cortical atrophy; the presence and severity of a "hippocampal lucency"; and overall temporal-lobe atrophy. Of those variables, hippocampal lucency showed the greatest sensitivity correctly identifying 82% of AD patients and also the greatest overall accuracy at 80%. The highest specificity was in the measure of ventricular volume. Small lateral ventricles correctly identified 85% of normal control subjects. George et al. suggest that in the absence of temporal-lobe atrophy, true normals are identified in 95% of cases; however, approximately 55% of cognitively normal elders show mild or greater temporal-lobe atrophy, and in that circumstance the subjective assessment of the size of the temporal lobes yielded only a modest 76% accuracy in distinguishing between normal and AD subjects. George et al. (1990) suggest that MR imaging with ability to provide improved visualization of the temporal lobes offers important advantages for further study of the temporal lobes in both AD and normal aging.

NEUROLOGICAL DEFICITS IN AD

Perhaps the most complete single study of neurological deficits in AD was conducted by Galasko, Kwo-on-Yuen, Klauber, and Thal (1990). They compared four groups of AD patients, very mild, mild, moderate, and severe with normal controls. Galasko et al. found, in the DAT groups, a significant association (at the 1% level) with rigidity, stooped posture, impaired graphesthesia, face-hand test, and glabella, grasp, and snout reflexes. Also common but not significant at the 1% level were cogwheeling, mask facies, gait abnormalities. The prevalence of abnormal findings increased with severity but only grasp reflex, impaired graphesthesia, and the face-hand test were significantly associated with severity of cognitive impairment. Rigidity and glabella reflex were the only neurological findings that were significantly

higher among patients with very mild AD as compared with controls. Galasko et al. conclude that there are few abnormal neurological findings in the early stages of AD.

NEUROPSYCHOLOGICAL DEFICITS IN AD

The deficits noted in this section provide a brief overview of deficits found in DAT. Subsequent chapters will examine a number of the most significant deficits in greater detail.

General Ability

Martin et al. (1986) report the depression of both Verbal and Performance Intelligence in DAT, with Performance Intelligence (visuomotor skills) more severely affected than verbal abilities.

Attention/Concentration Deficits

Haxby (1990) found impaired ability to maintain attention to complex or shifting sets follows second to memory impairment in AD.
He found that as a group 10 patients with mild DAT differed significantly from normal controls on tests of complex attention and planning. The tests used included the Trail Making Test, parts A and B, the Stroop Colour Word Test, and the Porteus Mazes.

Frontal Functions

Whelihan and Lesher (1985) examined the performance of three groups; cognitively normal 60-70-year olds (young-old), cognitively normal 76-92-year olds (old-old), and cognitively impaired 76-92-year olds on a number of tests believed to measure frontal functions. The frontal functions and tests included: (1) abstraction (WAIS Similarities), (2) inhibition (Stroop Test), (3) visuospatial integration (Hooper Visual Organization), (4) verbal fluency (modified Set Test), (5) sequential programming (modified dynamic organizational items from motor function section of Luria-Nebraska Neuropsychological Battery, (6) motor ability (modified finger tapping). They found that while frontal functions show greater impairment with age than do numerous nonfrontal higher cortical functions, there were significant

differences between cognitively intact old-old (76-92) and cognitively impaired old-old.

Spinnler and Della Sala (1988) described "frontal functions" under "control functions", and described the major functions as "attention and intelligence" (p. 263). The attention tests are described as the "selective type", and Spinnler and Della Sala list Attentional Matrices, Gottschaldt's Hidden figure Test, "the go\no go type (Reversal Learning, a standardized version of Luria's classical prefrontal test)," and finger agnosia testing. The tests of "intelligence" were nonverbal. The set of nonverbal intelligence tests includes abstract thinking (Weigl's Sorting Test), spatial planning with spatial load (Elithorn's Perceptual Maze Test), and logical tasks (Raven's Progressive Matrices). A verbal conceptualization measure was also included. Spinnler and Della Sala found that among DAT patients

> Performances on the tests of control functions are more often impaired with respect to the 'instrumental functions', such as memory, language, praxis, visual perception and spatial cognition. The largest number of patients scoring 0 (above 70% in this series) is found in Elithorn's Perceptual Maze Test and Gottschaldt's Hidden Figures Test. This is probably because these tests share two components, a spatial one combined with either planning or selective attention. They test the function of the posterior parietal region and the multi-modal function controlled by the prefrontal executive areas, which are both encroached on early in the disease (p. 263).

In his 1990 study, Haxby also found that patients with mild DAT were significantly different than controls on tasks demanding complex attention and planning.

Language

Spinnler and Della Sala (1988) also examined language changes in DAT. In their paper, they described language deficits under "left-hemisphere disorders" and they report two studies, a cross-sectional study (N=55) and a longitudinal study (N=32). The language tests used called for either oral comprehension (token Test) or for "access to inner lexicon" (word fluency on semantic cue) free word association and sentence generation beginning with two nouns. They found in the cross-sectional study that "roughly half of the

subjects scored below the fifth percentile of the healthy population on all of the language tests" (p. 262). Separate results for the longitudinal study are not reported. Spinnler and Della Sala argue that their results demonstrate that "left hemisphere involvement is frequent and early and particularly apparent on tasks that test access of the inner lexicon and require the verbally organized and purposeful complex of language" (p. 262).

At initial testing "nearly all" of Spinnler and Della Sala's patients could be classified in the Wernicke or amnestic or transcortical sensory aphasia category, and at retest 12 months later all were found to be aphasic and nearly all could be classified under the Wernicke or amnestic label. They report that soon after impairment on word-generation tasks begins, anomia becomes the most obvious finding in spontaneous speech and on visual confrontation naming, and that in the early stages semantic errors are more frequent than morphological or syntactic errors. Reading aloud and oral repetition deteriorated much more slowly. "Empty" and circumlocutory speech were "striking" early features in their DAT patients. Written language is more severely impaired than oral language, and they suggest that writing praxis and reading comprehension are possibly the most disordered features of language processing. They conclude that "testing for language is one of the most fruitful approaches to the longitudinal studies of AD, since it is feasible for longer than most other forms of cognitive testing," but caution that "the distinction between focal pathology causing aphasia and AD with an aphasic component still remains impossible on language examination alone" (p. 262). Spinnler and Della Sala comment that non-verbal communication which appeals emotional responsiveness and "stereotyped patterns of everyday behaviour" are far longer preserved in the course of the illness than any form of verbal intercourse.

There is an extensive literature on language deficits in DAT. While language deficits are neuropsychological deficits, the extent of the literature merits treating language deficits in DAT more completely as a separate entity in this review.

Nonverbal Abilities

Martin et al. (1986) noted marked individual differences with regard to word finding ability in comparison to visuospatial and constructional skill.

Some DAT patients showed greater impairment of language, while others manifested greater impairment of visuospatial ability and constructional skills. Nonverbal or perceptual abilities are described by Spinnler and Della Sala (1988) as right hemisphere disorders. They comment that among DAT victims, poor visual perception is not, with the possible exception of failure to associate a well-known face with its name or even recognize it as familiar, usually an early everyday report, and that "Among pseudofocal onset patterns of AD, patients with a predominantly visuospatial impairment rank about 3%" (p. 262), while predominantly memory and language patients ranked about 10% each. They do, however, cite Moore and Wyke (in Spinnler & Della Sala, 1988) and comment that

> AD patient's drawing and copying abilities are severely disturbed and that their performances differ qualitatively from those of focal hemisphere-damaged patients; patients with left focal deficits present constructional apraxia because of impaired planning and those with right focal deficits because of hampered reproduction of spatial relations, whereas AD patients omit essential features from their drawings, which are often small and cramped; in our series there was frequent evidence of the 'closing-in' phenomenon (p. 263).

Memory

The following is a brief overview. Memory changes and characteristics of memory in DAT will be treated more fully in subsequent chapters of this review.

Bayles, Boone, Tomoeda, Slauson and Kaszniak (1989) report that a "prominent feature of AD is the impairment of episodic memory . . . AD patients typically cannot recount events that happened in their recent past", and that "Whereas normal subjects forget an average of only 4% of the information they provide at first retelling, mild AD patients forgot over 98%" (p. 54). Haxby (1990) asserts that "memory impairment was often the first symptom followed by impaired ability to maintain attention to complex or shifting sets" (p. 109), and he argues that memory impairment is "usually global and severe" while non-memory impairment varies markedly from patient to patient.

Haxby further reported that the ability to commit *new* information to long-term memory was consistently and globally impaired in mild DAT while non-memory functions were not significantly impaired compared to controls. And, as previously noted, he suggests that memory impairment precedes neocortical metabolic abnormalities in DAT. Martin, Brouwers, Lalonde, Cox, Teleska, and Fedio (1986) describe memory impairment as a"universal feature of AD". They found relatively greater impairment of learning and memory in DAT patients in comparison to other cognitive functions, and that memory was more impaired regardless of the type of material presented. Liston (1979) found that the most consistent symptom of DAT, longitudinally, was impairment of memory, and reported that "impairment of memory is seen to be clearly the most consistent and frequent symptom [in DAT] over time" (p. 338).

Spinnler and Della Sala (1988) observe that amnesic phenomena of AD may be described under two headings: those belonging to the *anterograde episodic memory domain*, and those belonging to *retrograde performances*. In the anterograde episodic memory domain, AD patients show defects in activating long-term encoding and in the retrieval process such as supraspan learning and prose memory. There is also a "short-term anterograde component" as with "working memory" with "a rather selective impairment of the 'central executive' . . . coupled with a relatively intact phonological input store and articulatory loop and possibly a normal visuospatial scratch pad" (p. 261). Spinnler and Della Sala suggest that in the anterograde domain "there is evidence of intermingling of traditional amnesic defects . . . with a more general processing defect, such as impairment of the central executive (possibly related to the similarly proven damage to the prefrontal network and connections)" (Spinnler & Della Sala, 1988, p. 261). Retrograde performances are concerned with the rapid, quasi-automatic retrieval from semantic memory stocks and include the recall of autobiographical and public events and of organized overlearned information. Spinnler and Della Sala comment that while the anterograde defects found in AD are similar to those found in focal global amnesiacs, the retrograde defects are usually found in a subgroup of patients with frontal deficits. They emphasize the importance of memory impairment in DAT in the following statement.

> Dementia due to AD should be expected whenever a patient without clouding of consciousness has *progressive memory disorders* of insidious onset in everyday life (so-called 'everyday forgetfulness' or ongoing and prospective memory disorders), described by reliable informants, associated with *progressive left hemisphere disorders*, such as anomia in spontaneous speech and on confrontation naming, circumlocutory and 'empty' speech in a structured conversation or ideational apraxia, and/or with *progressive right hemisphere disorders*, such as topographical disorientation, dressing apraxia, prosopagnosia, etc (p. 259).

In their study, Spinnler and Della Sala found that on formal testing of DAT subjects, anterograde episodic memory is mildly to moderately deteriorated, e.g., verbal and spatial supraspan learning, tested by means of Buschke-Fuld's selective reminding technique and Corsi Blocks were severely impaired in over half of their patients. On Prose Memory assessed by immediate plus delayed recall of a long story, 85% of 26 mild and not aphasic DAT patients in their study performed below the 5th percentile of the normal population, and they assert that prose or story recall has been "proven to be the best predictor of everyday forgetfulness" (p. 260). They suggest that the power of Prose Memory or Logical Memory Passages arises from the fact that the task demands "the organized recollection of span-exceeding verbal information" (p. 260), and that because it requires the spontaneous generation of a task-specific strategy, it is sensitive to prefrontal damage.

Kaszniak (1988) cautions, however, that memory tasks that demand controlled, effortful processing are affected by high emotional arousal, depression, and normal aging as well as by dementing illness, and argues that recall tasks have been empirically shown to demand more processing resources than do recognition memory tasks. Kaszniak reports that recognition memory tasks demonstrate impairment in mildly to moderately demented DAT patients in comparison to age-matched healthy adults, and that while depressed patients may demonstrate recognition scores below those of age-matched controls, their error patterns are different from DAT patients in that they tend to show a conservative response bias while DAT patients endorse more false positives.

Spinnler and Della Sala (1988) describe procedural (or skilled) new learning as a "grey area" in AD patients. Some researchers have found evidence for preservation of procedural new learning while others have failed to do so, but they comment that most AD patients experience, in the late course of the disease, impairments of over learned manual skills, i.e., ideational apraxia. They note, however, that this "must not be listed as a strict memory failure" (p. 261).

This concludes the overview of neuropsychological deficits in DAT. As previously observed, while language deficits in AD are appropriately classified as neuropsychological deficits, the extent of the literature exploring that disorder warrants a more complete examination of that literature. That examination follows next.

LANGUAGE DEFICITS IN AD

Cummings, Benson, Hill and Read (1985) investigated 30 patients with DAT and 70 normal controls in a series of language tests and found the most abnormal language functions included the information content of spontaneous speech, comprehension of commands, naming, sentence completion, word list generation, writing to dictation, narrative writing, and completion of nursery rhymes. They found a more rapid decline in function when symptoms began earlier, and a consistent relationship between impairment of language and MMSE scores. Stepwise multiple regression showed three subtests, comprehension, narrative writing, and writing to dictation, accounted for 70% of MMSE score variation. Cummings et al. concluded that marked aphasic abnormalities and normal articulation early in DAT may help distinguish DAT from multi-infarct dementia in which prominent dysarthria and aphasia frequently coexist.

Bayles, Boone, Tomoeda, Slauson and Kaszniak (1989) assessed language deficits in 21 mild and 37 moderately impaired with DAT, 41 individuals with stroke-caused aphasia, and 31 elderly control subjects. Bayles et al. found that four tasks discriminated between normal elderly and mild DAT patients: Story-retelling delayed (60-75 min delay), a mental status task (similar to the Mental Status Questionnaire (Goldfarb & Antin cited in Bayles et al., 1989), Pantomime Expression--patients were shown a picture of a common object (book, saw, needle etc.) and asked to show how to use it, and the Peabody Picture Vocabulary Test. Using these measures, all subjects were classified correctly. A reading

comprehension total score best discriminated between mild and moderate DAT. Reading comprehension was followed by story-retelling immediate in discriminating those groups.

Naming was most severely impaired in DAT among five language functions measured by Western Aphasia Battery in an investigation by Huff, Corkin, and Growdon (1986). They also found a strong correlation (0.79) between impaired naming and impaired category fluency in DAT. Category fluency was more impaired in DAT relative to normals than naming. In one experiment, the difference between healthy control subjects and DAT patients was significant at $p < .001$ for category fluency but at only $p < 0.5$ for naming. Huff et al. designed different experiments to reduce the impact of impaired visual perception on naming. Their results suggested that for those in the early stages of AD who do not have unusual visual perceptual deficits, the naming difficulties lay with semantic rather than visual processing.

Kirshner, Webb, and Kelly (1984) also looked at perceptual difficulty, word frequency, and, as an additional variable, word length. They found that the confrontation naming deficit in their patients appeared to involve both perceptual and linguistic factors. Naming was best for objects and deteriorated with each step from objects to photographs, photographs to drawings, and drawings to mask drawings. Word frequency, but not word length also influenced naming performance. Contrary to Huff et. al., Kirshner et al. found "The naming errors made by both our demented and normal subjects were most commonly perceptual; i.e. names of objects similar in appearance to the stimulus," and concluded "Our data would suggest that both the perception and word-search stages of naming are impaired in demented subjects" (p. 29).

Somewhat different results were obtained by Bayles and Tomoeda (1983). They point out that normal controls made more perceptual errors than DAT patients in the study by Kirshner, Webb, and Kelly (1984). (The apparent confusion in dates results because the Kirshner et al. paper was originally presented, in part, at the American Academy of Neurology in 1982, and it is that presentation on which Bayles and Tomoeda base their comments.) Bayles and Tomoeda note that the majority of visually similar erroneous responses were also semantically related--71% of DAT compared with 100% for Parkinson's, 75% of Huntington's, and 100% for MID. The mildly demented patients in their study performed like

normals, "but moderately demented Alzheimer's disease patents made significantly more errors than normals and 92% of the misnaming made by dementia subjects were related in some way to the stimulus" (p. 110), and, they argue, "In general, the response to the stimulus was most likely to be semantically related, specifically, the name of an other item in the same semantic field. If in dementia patients the visual signal is degraded, it seems reasonable that the errors would be more random and related semantically to the stimulus only by chance" (p. 110). However, Bayles and Tomoeda's investigation did not, as Kirshner, Webb, and Kelly point out, "study perceptual difficulty as a variable and did not explore the effects of perceptually degraded stimuli" (p. 29).

Shuttleworth and Huber (1989) undertook a longitudinal study of naming disorder in dementia. They found that although linguistic errors were most common, perceptual recognition errors were not limited to late stages of disease. The percent of correct responses to 47 drawings declined with time in all patients, but at different rates for individuals. A less prominent decline in the ability to name real objects was also apparent. Shuttleworth and Huber also included category naming and controlled word association tasks, but their results did not conform to reports in earlier studies of better performance on category naming than on controlled word association tasks early in the course of the disease. The degree of dementia, as determined by MMSE scores, did not explain difference in verbal fluency. Shuttleworth and Huber report that their patients were more commonly able to retrieve phonemically related than semantically related words within the time limits. Review of the Shuttleworth and Huber study appears to suggest that, in general, the proportion of individuals showing primarily semantic errors and the proportion showing primarily perceptual errors parallel the percentages found in other studies of individuals with DAT showing early impairment of language function and those showing early impairment of perceptual function.

Martin and Fedio (1983) administered tests of "word production"--naming and fluency--and comprehension of single words to 14 mild DAT patients and age and education matched normal controls. Word comprehension was rated on (1) broad category judgement by giving the patients 10 pleasant words, 10 unpleasant words, and 10 neutral words and asking them to rate the words on a scale of 1-7 from "very unpleasant" to "very pleasant", and on (2) a "symbol referent test" which required the patients to chose which of four abstract drawings best represented

the meaning of the word printed on the same page. The abstract or "nonrepresentative" drawings were of four word types, objects, actions, emotions, and modifiers. The word production measures were from The Boston Naming Test (BNT) and the fluency measure from the Mattis Dementia Rating Scale. Martin and Fedio's results showed that DAT patient performed more than 3 SD below the mean of normals on the BNT. DAT patients were also impaired on comprehension of objects, actions, and modifiers as measured by the Symbol Referent Test but performed in the normal range on the Vocabulary and Similarities subtests of the WAIS and on judgments of affective meaning of the Symbol Referent Test.

On BNT, Martin and Fedio's DAT patients often substituted either a more general, higher order term, or the name of an object from the same semantic category indicating a tendency to produce "semantic field errors involving either a hierarchical relationship or a linear, within category relationship, similar to the responses of aphasic subjects with lesions in the posterior left hemisphere" (p. 137). The fluency test revealed a particular difficulty in producing names of items within a category with relatively preserved ability to produce more general categorical items. DAT patient's performance on rating words for degree of pleasantness was "indistinguishable from normal subjects". Martin and Fedio conclude that "Taken together, these findings suggest that AD may result in a reduction in the availability of the set of attributes that determine word meanings. Apparently, at least in the relatively early stages of the disease process, knowledge of enough attributes is available to allow for the proper categorization of related items, but not clearly distinguish between them" (p. 138). However, that conclusion is drawn in the face of their own observation that DAT patients have "relative preservation of the ability to adequately define words using appropriate descriptive phrases (Vocabulary) and knowledge of category membership (Similarities)" (p. 138).

Verbal fluency in DAT was also examined by Rosen (1980). Rosen examined fluency, animal naming and C, F, and L words, in 10 mild SDAT, 10 Moderate-to-Severe SDAT, and 10 normals. She found that normals and mild dementia retrieved more animal names than "CFL" words, and that compared to normals, mild dementia subjects showed greater decrement on "CFL" words than animal naming while Moderate-to-Severe dementia subjects showed no difference between the tasks. Rosen suggests that best explanation is that "the hierarchical organization and the different internal structures of the categories used in the present study

influenced retrieval. The hierarchical organization among categories appears as supersets of a given category, the category itself, and subsets of the category" (p. 143). She maintains that the internal structure of the semantic categories consists of a "core meaning" composed of the "clearest cases" or the best examples of the category. The hierarchical structure facilitates entrance into the category and once in the category subset retrieval is facilitated. With "CFL" words immediate entrance into the category leads to fewer words because there are few "clearest cases".

Butters, Granholm, Salmon, and Grant (1987) obtained contrary results. Their mildly impaired DAT patients were impaired on a category fluency measure, but were not impaired in their ability to generate words beginning with a specified letter. They suggest that the performances of the DAT patients is affected by language dysfunction and increased sensitivity to proactive interference.

Rapcsak, Arthur, Bliklen, and Rubens (1989) investigated lexical agraphia in AD and found that SDAT patients spelled regular words and nonwords as well as controls, but that the DAT patients were significantly worse when they spelled irregular words. Rapcsak et al. suggest that lexical spelling system, as opposed to the phonological system, is impaired in DAT.

The phonological system utilizes sound-letter correspondence or phoneme-grapheme conversion rules and is predominantly used when spelling orthographically regular words while the lexical system utilizes a whole-word retrieval process and requires consultation of internal memory store of learned spellings. Rapcsak et al. state that it is believed that word representations in the orthographic lexicon are in the form of visual word images, and that their findings suggest a loss of word representations from the orthographic lexicon in SDAT and/or an inability to access the representations of whole words, that is they suffer from lexical agraphia. They note, further, that lexical agraphia is associated with damage to the left tempero-parieto-occipital region and especially with focal injury to the junction of the angular gyrus with the parieto-occipital lobule, and that the degenerative process in DAT affects the multimodal association cortex of the tempero-parieto-occipital junction most severely and consistently while the immediate perisylvian language areas (especially the supramarginal gyrus and insula) are relatively preserved reflecting the preserved phonological and syntactic abilities in DAT.

Reduced receptive vocabulary, impaired word fluency in a category, and difficulties in providing concise definitions in DAT patients were confirmed by Hier, Hagenlocker and Shindler (1985). They found that during narration or spontaneous discourse DAT patients manifest difficulties in lexical access exhibiting "circumlocutions, semantic paraphasias, use of empty words, use of vague superordinate or generic words in place of words with more precise meanings, and explanatory paraphasias" (p. 120). In their study, DAT subjects showed greater impairment of lexical diversity than in syntax.

Nebes, Boller, and Holland (1986) investigated the use of semantic context by patients with DAT. They found that DAT patients performed relatively normally in situations in which there were few demands on attentional capacity or demands for effortful processing and that in a category-decision task DAT subjects did not show disproportionate loss of weaker associations. They did find, however, that demented subjects were differentially impaired in deciding whether a nonexemplar was a member of a given category. Nebes et al. suggests this could indicate that the patients have a specific problem in making category-exclusion decisions, but that it could also suggest a more general decision-making deficit. As evidence of the latter, Nebes et al. points out that DAT patients were disproportionately slower than normals on a simple task of deciding whether a certain letter was present in a visual display when a negative response was required. They concluded that "it appears that the performance of demented patients may in some cases actually be more dependent on the constraints imposed by semantic context than is that of normal subjects. In situations in which the context restricts possible responses to a few items, demented patients perform relatively normally. When, however, the contextual constraints are small or are actually misleading, their performance deteriorates markedly" (p. 269).

In another study, Nebes and Brady (1988) examined the premise that DAT patients retain general semantic knowledge about concrete objects but lose information about object's distinctive features and functions. To test that hypothesis, subjects were given a concrete "object" (a line drawing with the object's name printed under it) and a series of words including distactors and were then asked to say which of the words were related to the concrete concept. The target words were the object's superordinate category; a verb describing an action or function characteristic of the object; a distinctive physical feature; a general associate of the object; and the name of the object itself. Nebes and

Brady found that it did not take DAT patients disproportionately longer to make decisions about physical features and actions than about superordinate categories and general associates. They concluded: "the present results do not show the field of semantic attributes aroused by presentation of a concept to be diminished or constricted in Alzheimer patients" (p. 15).

Nebes and Brady acknowledge that their results do not agree with those of Martin and Fedio (1983) but point out that in their study patients were asked explicit questions about the properties of a pictured object which required the patients to carry out a directed search of a concept's semantic field for a specific attribute. In exploring reasons for the discrepant results, Nebes and Brady consider that "the degree to which a task requires retrieval of specific information might . . . be important in determining whether or not demented patients demonstrate knowledge of concept attributes" (p. 15).

This review of language deficits reveals that despite preserved "social language" in mildly and moderately impaired DAT patients, significant impairment of a number of language functions arise early in the course of the disease and deterioration of language continues throughout its course. As previously observed, language deficit falls within the broader range of neuropsychological deficits that may contribute to the diagnosis of DAT, and with this review of language deficits, the review of neuropsychological deficits in the diagnosis of AD is closed. There remains, yet, one area in the diagnosis of DAT to be explored, and that is the nature of psychiatric changes in DAT.

PSYCHIATRIC DISORDERS IN AD

Liston (1979) listed a total of 72 discrete and relevant symptoms recorded as having been present as some time during the course of the illness (AD) from onset to diagnosis. The most frequent symptom found was an observed change in personality or behaviour, though that symptom is not further delineated. Liston found that depression ranks second in frequency at both onset and diagnosis but fifth in frequency over entire course of disease while apathy was the third most frequent symptom at illness onset but only eighth among symptoms ever experienced. Overt manifestations of psychosis were noted in only 5/50 patients. The psychotic manifestations include: auditory hallucinations and persecutory delusions; visual hallucinations and paranoid ideation; visual and auditory hallucinations; paranoid thinking; and hallucinations. Terry and Katzman (1983)

report that about 10% of patients referred with an initial diagnosis of dementia are found to have "pseudodementing functional illness".

Observed change in personality or behaviour is described more completely in Teri et al. (1990) under the label "behavioral disturbance". Behavioral disturbance includes, but is not limited to, difficulties with personal hygiene and care, depression, agitation, aggression, and wandering. Estimates of such disturbances vary but behavioral problems affect between 70 and 90% of patients with dementias. Agitation ranks as one of most often cited reasons for treatment with neuroleptics in nursing homes but agitation rarely presents alone; usually the agitated patient also exhibits signs of aggression, psychosis or exacerbation of underlying confusion. Assaultive or aggressive behaviour, either physical or verbal, is a significant behavioral component for many demented patients. Physical, aggressive behaviour is reported in 25% to 51% of both community-dwelling DAT suffers and patients on inpatient geriatric units. There are no consistent prevalence figures for screaming but it is thought to occur in 45-50% community-dwelling dementia patients at some time or the other, in 15-25% at least once a week, and for 5-10% it is a daily problem. Wandering is another significant concern. Estimates vary with population studied, but it is thought to occur in 4-26% nursing home residents and in up to 70% of community-residing patients. Depression is a prevalent, persistent and often devastating problem for patients and care-givers according to Teri et. al. Approximately 30% AD patients meet criteria for diagnosable depressive disorder and individual symptoms of depression appear in as many as 86% of patients with AD.

In another study, Teri, Borson, Kiyak, and Yamagishi (1989) examined 56 community-residing AD patients across three domains of function: behaviour, cognition, and activities of daily living. They reported their findings in terms of the relative occurrence of problems that present more than twice per week as reported by 56 caregivers. Difficulties with the highest occurrence were loss of memory, particularly for recent events, 84%; confusion 82%; and disorientation for time, place and/or person 64%. Other disorders reported to have "substantial occurrence" are underactive, moves very little 43%; tense, jittery, or nervous 34%; loss of interest in activities 32%; unusually sad and depressed 24%; apathetic 21%; preoccupied with a specific bodily system 20%; excessive appetite 20%; follows strict rituals in behaviour 20%; and awaken early (before 5 a.m.) 20%.

Teri, Hughes, and Larson (1990) found that AD patients with health and behavioural problems declined at rate between 1.4 and 5 times faster than patients without those problems. Health problems included thyroid disease, head trauma, gait disturbance, and alcohol and drug abuse. Alcohol abusers appeared to decline most quickly.

Mackenzie, Robiner, and Knopman (1989) investigated different rates of depression obtained for patients with AD depending on whether patient or family interviewed. Data from 36 patients yielded a depression rate of 13.9% while information from families yielded a rate of 50.0%. The great majority of disagreements (19/36 cases) occurred when patient stated he or she was not depressed while family provided information to the contrary. Families more frequently endorsed patient's loss of interest or pleasure, irritability, fatigue, and feelings of worthlessness than did patients. Mackenzie et al. report that estimates in prevalence of depression in AD range from 12.7% to 57%, and suggest the variance in prevalence reported may be partially due to differences in recruitment practices, assessment methods, diagnostic criteria, and length of follow up.

"Alzheimer's disease is the most widely encountered cause of psychiatric pathology associated with a specific neuropathic substrate" (Merriam, Aronson, Gaston, Wey, & Katz, 1988, p. 7). Merriam et al. considered difficulties in distinguishing depressive symptoms in DAT from a clinically recognizable depressive syndrome in an organically impaired population, and found that investigators have called particular attention to problems in the interpretation of vegetative indicators common to both dementia and depression. The reports of prevalence differ significantly; from approximately 19% (in "less severely demented individuals") to 40% in other studies. Merriam et al. looked at a sample of 175 subjects with a mean age of 72 years and moderate severity of dementia overall. Behavioural data was obtained from a structured caregiver interview.

The results obtained by Merriam et al. indicated depression in 86.9% of sample. Dysphoria/depression was determined by a positive response to inquiries regarding depression, sadness, fearfulness, excessive worrying, or hopelessness. In their sample, 92.6% were judged to exhibit loss of interest or pleasure, and 97.1% of individuals responded affirmatively to at least one inquiry in the categories required to meet criterion A of the DSM-III for depression. Criterion

B for depression in the DSM-III requires the persistence for at least two weeks of four of eight associated symptoms which are heavily loaded with neurovegetative phenomena. At least four of those symptoms were exhibited by 86.9% of sample. Of the total sample, 85.7% fullfilled the DSM-III criteria for a major depressive episode, that is they met both A and B criteria. However, 89.8% of patients who otherwise met the criteria for major depressive episode were either always or frequently capable of being distracted or cheered by their caregivers. Merriam et al. suggest that finding may mean that such individuals, while exhibiting depressive symptoms, are not syndromically depressed, and that major depression is a false-positive diagnosis. They found a significant positive correlation between age and number of vegetative symptoms, but no significant correlation between the dementia severity score and number of those symptoms.

Merriam et al. also investigated psychomotor dysregulation, perceptual symptoms, and paranoia in their sample. With regard to psychomotor dysregulation, 61.1% of the sample were reported to have been episodically agitated within 2 weeks prior to interview. The tendency for psychomotor dysregulation did not correlate with either severity of dementia or presence of major depression, and appears to be a property of actually having the disease rather than its stage or associated depressive symptomatology. Results obtained in the investigation of perceptual symptoms identified two separate disorders of perception in AD: (1) capacity to organize perceptual information in the environment is compromised, leading to disorientation and misrecognition of stimuli; and (2) subjective mental phenomena are accepted as real. Their results indicated that 49.1% of the sample failed to recognize important others or mistook strangers for familiar others; 41.7% misidentified familiar places; and 17.1% exhibited a Capgras-like phenomena. The second form, accepting subjective mental phenomena as real, was exhibited by 28% of the sample in the form of auditory or visual hallucinations. Various perceptual disorders were strongly related to severity of dementia but not to the presence of DSM-III major depression. Paranoid elaborations of a relatively minor nature such as blaming others for missing or misplaced possessions appeared in 42.3 % of the sample. In 56.0% of the sample more severe paranoid symptoms such as persecutory or self-referential ideation appeared. The tendency to blame, but not the more serious paranoid symptoms, significantly correlated with the presence of DSM-III

depression. No meaningful correlations between paranoid phenomena and severity of dementia were observed.

In a review of 30 studies, Wragg and Jeste (1989) found that depressive and psychotic symptoms occurred in 30%-40% of AD patients, and that isolated symptoms were two or three times as frequent as diagnosable affective or psychotic disorders. They suggest that investigators must consider that both AD and isolated psychiatric symptoms are relatively frequent in elderly persons, and that one should expect that in some individuals they would be superimposed. Wragg and Jeste observe that it is also possible that the affective or psychotic symptoms, or both, arise as a manifestation of a common pathophysiology attributable to AD itself and that the symptoms do not necessarily occur coincidentally or in reaction to cognitive deficits.

That observation is not, however, supported in a study by Zubenko, Moossy, and Kopp (1990) who investigated neurochemical correlates of major depression in dementia. Their study involved 37 demented patients (including multi-infarct and other dementias) with and without depression and 10 controls with no history of dementia or depression. Zubenko et al. found that demented patients with major depression exhibited a 10-20 fold reduction in the level of norepinephrine in cortex, along with relative preservation of choline acetyltransferase activity in subcortical regions. They concluded that their "results indicate that the development of major depression in primary dementia is associated with a profile of neurochemical changes that are qualitatively distinct from those associated with primary dementia" (p. 213).

Petry, Cummings, Hill, and Shapira (1989) conducted a follow up study of 19/30 DAT patients at three years after initial assessment. The mean age of patients at last testing was 72 years. The mean patient MMSE score at initial assessment was 10.9 and had declined to 2.8 at last testing. Petry et al. distinguished four patterns in their follow up study. The first pattern was of a marked difference between the premorbid profile of behaviour and personality assessment obtained after the onset of illness on 12 of 18 dimensions with patients being " more out of touch", reliant on others, childish, listless, changeable, unreasonable, lifeless, unhappy, cold, cruel, irritable, and mean compared with controls. The second pattern showed a continuous progression in behavioural change with significant differences across three scores, listlessness, insensitivity, and coldness. In the third pattern there was nc

change at any time in the disease between first and second assessments. The fourth pattern revealed that some behaviours had appeared then regressed over the course of illness. Four items showed a trend toward reversal: excitable/calm, stable/changeable, easygoing/irritable, and happy/unhappy.

The review of psychiatric disturbances in AD reveals that although DAT patients present with a variety of psychiatric disorders, there is significant variation in that presentation among different individuals. For the most part, individuals in the early stages of the disease present with few or vague disturbances in personality or behaviour. With regard to diagnosis, depression is most problematic as the rates of both depression and DAT in elderly persons are high. Differential diagnosis is further complicated by the appearance of neurovegetative symptoms with both depression and DAT, and that difficulty is explored further in the next chapter which focuses on the problems of differentiating AD from other dementing disorders.

CHAPTER SUMMARY

This chapter has reviewed factors contributing to the difficulty of the clinical diagnosis of DAT and laboratory techniques used in clinical diagnosis. Characteristic neurological, neuropsychological, language, and psychiatric disorders in DAT were also examined.

Factors contributing to the difficulty of clinical diagnosis include the heterogeneous presentation of the disease and the absence, until recent years, of clinical and histopathological criterion for the diagnosis of DAT and AD. Discussions of laboratory techniques included examination of body fluids, especially CSF and imaging of both cerebral physiology (electro-physiology, regional cerebral blood flow, position emission tomography, single positron emission computerized tomography) and cerebral structure (computerized axial tomography and magnetic resonance imaging).

Neurological disorders in AD were briefly reviewed as were a number of neuropsychological deficits. Neuropsychological deficits reviewed included general ability, attention/concentration, frontal or control functions, language, nonverbal abilities, and, briefly, memory. Because of the extensive literature on language deficits in AD, language deficits were examined more thoroughly in a separate discussion. Finally, psychiatric disturbances in AD were examined.

Memory is, in the view of many investigators, the hallmark of AD, and memory impairment is the focus of this investigation. The memory deficits reviewed in this chapter provide but a brief overview of memory deficits in AD, and separate chapter is devoted to the examination of memory in AD.

CHAPTER 4

REVIEW OF THE LITERATURE--ISSUES IN DIFFERENTIAL DIAGNOSIS

AD SUBTYPES

Differential diagnosis of AD will be influenced by a whether a clinician believes AD is homogeneous in its presentation or heterogeneous. If one believes "AD does not necessarily result in a single behavioral syndrome" (Martin, 1986, p. 607) the clinical diagnosis of AD becomes more difficult as one must admit an extended range of signs and symptoms as indicative of early manifestations of the disease.

A Brief Overview

Capitani, Della Sala, and Spinnler (1990) discuss "controversial neuropsychological issues in AD" and include in their discussion the issues of onset-age and hemispheric asymmetry of impairment. They note that the progression rate of neurodegenerative disorders shows great interindividual variability, but assert that it is "generally held" that the progression rate is more rapid when the clinical onset is earlier. Research findings have yielded equivocal evidence; some have supported the clinical impression of more rapid progression of cognitive impairment with early onset while others have not, but according to Capitani et al. the belief that early onset portends more rapid progression "has not stood up to the epidemiological and histopathological evidence through time" (p. 133). Research investigating hemispheric asymmetry has also provided contradictory results. Capitani et al. conducted two studies in an effort to contribute to the resolution of these issues.

Early Onset Versus Late Onset

Capitani et al. (1990) studied 52 mildly demented DAT patients (all right handed). An impressive neuropsychological battery was administered that examined attention, intelligence, memory, language, spatial cognition, and visual perception. For all 21 tests used in the battery, procedures and healthy age-, education- and sex-adjusted norms for the Italian population were available. They comment that on the basis of the study, "evidence is provided that the earlier the behavioral onset the more severe the overall

cognitive impairment" (p. 138). Capitani et al. conclude: "Our findings confirm that the earlier the behavioral onset of Alzheimer's disease, the more severe the cognitive impairment, and that cognitive impairment is greater for LH [left hemisphere] than for RH [right hemisphere] abilities, irrespective of onset-age" (p. 139). They caution, however, that "This conclusion is confined to patients having a mild severity of dementia, a rather short length of illness (slightly longer than 2 years . . .), and not being older than 70-year [*sic*] at the testing time." (p. 139)

In another investigation, using a much weaker set of instruments, Chui, Teng, Henderson, and Moy (1985) investigated age at onset, aphasia, family history, and motor disorder. Chui et al. determined the severity of illness with Mini-Mental State Exam (Folstein et al. cited in Chui et al., 1985), an informant response to Everyday Activities and Habits subscales of Blessed-Tomlinson-Roth Dementia Scale and Global Deterioration Scale. Their findings indicated that earlier age of onset was associated with greater language difficulties as determined clinically and by the MMSE language score; that there was no significant difference for any variable studied in patients with "strong family histories" (two or more secondary cases) and patients with negative family histories; and that there was no difference in duration of illness for patients with or without extrapyramidal signs. With regard to early-onset and aphasia, they found that language disorder usually follows memory loss, and that the prevalence and severity of aphasia correlated with duration of illness. Chui et al. comment that "The prominence of language disorder in early-onset patients may imply selective vulnerability of perisylvian areas for the pathologic lesions of early-onset Alzheimer's disease and selective vulnerability of limbic areas in late-onset patients" (p. 1548). They concluded that while their "findings support the contention that there are clinical subtypes of Alzheimer's disease . . . a cross-sectional study may show large variations in the expression of a degenerative disorder that do not necessarily reflect underlying biologic differences" (p. 1549).

Hemispheric Asymmetry

Martin et al. (1986) comment that while it is possible that from a neuropathic perspective a homogeneous group of patients may be found whose brains will reveal the "cardinal features of AD", "it has become increasingly clear that, from a behavioral standpoint, patients assigned a provisional diagnosis of AD will often exhibit disparate profiles of impaired and preserved cognitive abilities" and raise the question "whether a unitary, behaviorally definable syndrome of AD exists at all" (p. 595). To examine that premise, they investigated a sample 42 patients and compared them with a normal sample of similar age.

Martin et al. (1986) examined a stage model verses subgroup model; models which are not, they concede, mutually exclusive. The stage model assumes a relatively homogeneous deterioration of functions which is characterized by a *quantitative* increase in severity of symptoms over time with the possibility that *qualitatively* different types of symptoms will be manifest as the disease progresses. Subgroup models reject the premise of homogeneous, but not progressive, deterioration and posit separate "clusters of symptoms which define and differentiate patients, especially during the early stages of the disease process" (p. 595). They suggest that the subgroup model would have different implications and consequences for the early detection of AD.

Martin and his colleagues administered a comprehensive neuropsychological test battery which in addition to the Wechsler Scales and the Mattis Dementia Rating Scale included measures of attention; visual, auditory and tactile recognition; visuospatial and constructional skills; language comprehension, fluency, and naming ability; and learning and memory for verbal, nonverbal, and spatial information. They found that performance, averaged across all patients, demonstrated pervasive impairment of cognitive abilities, and the patient's performance was consistent with the "traditional descriptions" of patients AD, namely, depression of Verbal and Performance IQ with visuomotor abilities more severely affected than verbal abilities, and greater impairment of learning and memory relative to other cognitive functions. The majority of patients were impaired on learning and recall regardless of the modality examined but marked individual differences were

noted with regard to word finding ability compared to visuospatial and constructional skill.

Martin et al. sought to document their clinical impressions with additional testing and selected three tests from verbal and nonverbal domains. The verbal, or word finding, tests were a visual confrontation naming task, a categorical word generation task, and the "easy" paired-associate items from the WMS. The nonverbal tests included two measures of visuoconstructional ability, the Block Design subtest of the WAIS and the Rey-Osterrieth Complex figure (Osterrieth, cited in Martin et al., 1986), and a measure of visual pattern discrimination (Mosaic Comparisons Test, cited in Martin et al., 1986). Factor analysis using varimax rotation of principal-components failed to yield a general factor, but a 2-factor solution accounting for 70.5% of total variance did emerge. Factor I had high loadings for nonverbal tests with negligible loadings for verbal measures while Factor II loaded on verbal tests. Variance explained by Factor I, unrotated, was 48.2% and with varimax rotation 41.4%; Factor II, unrotated, accounted for 27.7% of variance, and with varimax rotation 29.1% of variance. In the correlation matrix, the strongest relationships were among nonverbal tests: BD and RCFT-copy .888, BD and Mosaics .834, and Mosaics and RCFT-copy .690. Verbal test correlations were Naming and Fluency .672, Naming and P-A easy .506, and Fluency and P-A easy .406.

A cluster analysis found five patient clusters. Martin et al. (1986) then evaluated cluster membership with linear discriminant analysis which successfully reclassified 41 of 42 patients. Three groups (subgroups) showed relatively equal deficits on all measures with group differences attributable to overall degree of impairment. The patients in these subgroups exhibited *qualitatively* similar patterns of impairment of cognitive deficit and, they assert, "conformed to the global, deteriorative stage model of the disease process" (p. 600). Two additional groups were identified: Group 2 (9/42) composed of patients with poor word-finding skills concurrent with relatively intact visual perceptual and constructional skills, and Group 3 (8/24) which showed "substantially greater impairments on visuo-constructive measures than on measures of word-finding." (p. 600). Martin et al. comment "the patient subgroups did not differ with regard to age or reported symptom duration . . .

suggesting that neither age at onset nor disease duration were major contributors to the observed patterns of impairment" (p. 600).

PET studies conducted by Martin et al. (1986) in conjunction with the research outlined above demonstrated that patients with relatively equal impairments of word-finding and visuoconstructive abilities . . . had relatively symmetrical and bilateral hypometabolism in the temporal and parietal regions. In contrast, patients with circumscribed word-finding deficits (subgroup 2) evinced lower metabolic rates in their left temporal region ($p<.001$) and patients with relatively focal visuoconstructive impairment (subgroup 3) had greater reduction of glucose utilization in the right temporal and parietal regions in comparison to all other areas ($p<.001$) (p.604-605).

Haxby (1990) administered an "extensive battery" of neuropsychological tests: Mattis Dementia Rating Scale, Mattis; Wechsler Adult Intelligence Scale, Wechsler; Wechsler Memory Scale, Wechsler; Trail Making Test, Reitan; Stroop Colour Word, Golden; Porteus Mazes, Porteus; syntax comprehension, Whitehouse; Controlled Word Association Test, Benton; Extended range Drawing, Haxby; and Block Tapping Span, Milner (all cited in Haxby, 1990). The tests measured, respectively, overall severity of dementia, memory, ability to sustain attention to complex sets, planning, language, and visuospatial function. They also used Positron Emission Tomography measuring regional metabolic rates for glucose (rCMRglc) in resting state (eyes covered and ears plugged). Fourteen neocortical regions, seven for each hemisphere were examined. Regions were prefrontal, premotor, orbitofrontal, sensorimotor, parietal association, lateral temporal and occipital cortices.

Haxby (1990) found equivalent numbers of patients have left-sided and right sided asymmetries, and approximately one-third of patients with DAT have symmetric rCMRglc values in all the association cortices. The frontal, parietal and temporal association cortices all demonstrate significantly increased asymmetry at all stages of DAT, indicating that all association cortices are affected throughout the course of DAT. (p. 113)

In the moderately demented DAT patients, the neuropsychological discrepancy between language and visuospatial impairments was "consistently and significantly correlated with right-left metabolic asymmetries" and all

were in the "expected direction" (Haxby, 1990, p. 115), that is, disproportionate language impairment was associated with left-sided hypometabolism and disproportionate visual-spatial impairment was associated with right-sided hypometabolism. In moderately demented DAT patients, "disproportionate frontal hypometabolism was associated with impairments of verbal fluency and simple attention (trail A), and disproportionate parietal hypometabolism was associated with verbal comprehension, calculations, visuospatial construction and immediate visuospatial memory span" (p. 115).

Mildly impaired DAT patients in Haxby's study did not demonstrate significant impairments in nonmemory cognitive functions, but they did demonstrate the same variably distributed association cortex metabolic reductions. Patterns of nonmemory language cognitive test scores among mild DAT patients were uncorrelated with the right-left rCMRglc asymmetries.

Capitani et al. (1990) also examined verbal-nonverbal differences and hemispheric asymmetries. They examined 47 DAT patients with tests of left- and right-hemisphere function. The left-hemisphere tests were Word Forward Span, Token Test, and Weigl's Sorting Test. Right hemisphere tests were Spatial Forward Span, Street's Completion Test, and a visual Length Discrimination Test. Capitani et al. found more severe impairment of left-hemisphere abilities, at least early in the course of AD. They note that there were patients who performed worse on right-hemisphere tests than left-hemisphere tests and suggest that these results indicate that the predominance of left-hemisphere deterioration was not a test artifact, i.e., that the left-hemisphere tests were not simply more sensitive.

Capitani et al. (1990) remind that their results are in line with CT-asymmetries, blood-flow SPECT-asymmetries and metabolic PET-asymmetries, all of which point to more frequent involvement of the left side of the supra-tentorial brain. They report that a "second line of evidence" in favour of an asymmetric hemispheric involvement is found in their previous research (Capitani, Della Sala, & Spinnler, 1986 cited Capitani, 1990) which indicated that language disorders were one of the most frequent "pseudo-focal onset features of AD." Among cases with a "'pseudo-focal onset' the most prominent symptoms were aphasia in 44.5 %, amnesia in 44.5% and spatial disorders 11%" (p. 140). In concluding, they comment

> The left-sided predominance of the AD process is possibly related to the healthy morphological and developmental asymmetries of the brain . . . In this context it is interesting to note that left-sided morphological . . . and electroencephalographic asymmetries . . . are enhanced by aging. . . This might suggest that at the onset the AD-process prevailingly affects cortical neurons that have some specific biochemical marker . . . and that such neurons are usually more numerous in the left than in the right hemisphere . . . possibly because of the larger extent of the cortex in some left peri-sylvian areas (p. 141).

These appear to be convincing demonstrations, but a clinician with a breadth of experience in intellectual assessment is aware that there are frequently wide differences in verbal and nonverbal abilities in normal individuals. Analysis of Verbal-Performance (V-P) differences for the WAIS and WAIS-R are difficult to find, but there is no compelling evidence that relative differences in verbal and nonverbal abilities change, for the vast majority of individuals, with maturation, and the normative sample for the WISC-R has been studied for those differences. Analysis of WISC-R normative group revealed that about 50% of children had V-P differences of 9 points, 33% had V-P differences of 12 points, and 25% had V-P differences of 15 points. (Kaufman, 1979) In this study, 21% had greater nonverbal abilities; 19% had greater verbal abilities; and 60% demonstrated relatively equal impairment of verbal and nonverbal abilities. It is not clear that Martin et al. (1986) did not find differences in "normal" range of verbal versus nonverbal abilities likely present since childhood. What is not examined among normal individuals with VIQ-PIQ differences is whether there are hemispheric metabolic differences. Such research might cast further light on the nature of hemispheric metabolic differences in AD.

Jagust, Davies, Tiller-Borcich, and Reed (1990) present a case which they identify as "focal Alzheimer's disease." They present single case study of presenile onset dementia accompanied by a slowly progressive hemiparesis. Autopsy examination showed severe pathologic involvement of the right somatosensory cortex with neuritic plaques and neurofibrillary tangles in addition to degeneration of the nucleus basalis and locus ceruleus. Postmortem autopsy found the patient's brain was "severely atrophic."

Whether this was yet another subtype of AD or AD at all appears open to question. It is important to note that their patient, a woman, developed initial symptoms at age 63 which were demonstrated through a series of motor vehicle accidents believed to attributable to problems of judgment and coordination. She was able to work as a secretary for another 4 years after the initial observation during which time she became progressively more cognitively impaired and also stopped using her left hand. She was also diagnosed with hypertension at age 67 (though MRI or autopsy did not reveal evidence of cerebral infarction). When she was first seen by a neurologist at age 68 she had mild to moderate dementia. At age 72, she was severely demented (MMSE score 9/30) and had marked expressive language impairments, perseveration, and visuospatial deficits. Her spontaneous speech was "empty" and dysfluent with word-finding difficulties and literal and verbal paraphasias. Autopsy did reveal NP and NFT, with the NFT predominating especially in the deeper cortical layers and in the hippocampal pyramidal cell neurons. However, it has already been shown that the accumulation of NP and NFT are present in normal aging and other disorders as well as in AD. There is some danger in describing any dementing disorder in which NP and NFT are present, regardless of history, as AD.

The studies supporting the premise that there are subtypes in AD are compelling, but until there is further study of normals who manifest strong individual differences in verbal and nonverbal abilities and of the relationship to premorbid verbal and nonverbal abilities to subsequent patterns of impairment in AD, one is obliged to have some reservations with regard to verbal and nonverbal subtypes of AD. The studies of AD subtypes do, however, caution the clinician that the presentation of AD is heterogenous, and that heterogeneity increases the difficulty of differential diagnosis of AD. The differential diagnosis of DAT and MID is a case in point.

DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE AND MULTI-INFARCT DEMENTIA

Hagberg and Gustafson (1985) examined differential diagnosis among DAT, MID and dementia with a fronto-temporal accentuation of cortical degeneration (DFT). They examined verbal ability, reasoning ability, verbal memory, spatial memory, intellectual speed, and motoric speed in their clinical groups. They found that DAT was characterized by relatively preserved verbal

ability, moderate declines in intellectual and motoric speed, with greatest declines, to about same level, for reasoning ability, verbal memory and spatial memory. Among DFT patients, performance in all areas was below mean test scores. The best score in the DFT group was, perhaps somewhat surprisingly, on reasoning ability. They had moderate declines in verbal and spatial memory, but their lowest scores were on verbal ability, and intellectual and motoric speed. MID patients showed relative preservation of verbal ability, reasoning ability, and intellectual and motoric speed; mild to moderate declines of spatial memory; and greatest declines on verbal memory, but with considerable variation due to acuteness and localization of lesions. On the basis of their study, Hagberg and Gustafson conclude that it is possible to form a differential diagnosis of AD on clinical data.

Liston and La Rue (1983a) undertook a critical analysis of representative clinical studies and articles published over the past two decades on the differential diagnosis of primary degenerative dementia and multi-infarct dementia. The features of MID, as set forth by Roth 1955 (cited in Liston & La Rue, 1983a) are (1) dementia associated with focal signs and symptoms indicative of cerebrovascular disease or (2) a remittent or markedly fluctuating course at some stage of the dementing process combined with any one of the following features: emotional incontinence, the preservation of insight, or epileptiform seizures. They also note the importance of the Hachinski Ischemic Scale (Hachinski et al. cited in Liston & La Rue, 1983a) in attempts to differentiate DAT and MID. Liston and La Rue (1983a) report that there are

> three features common to all of these classification schemes [for MID]: first, a dementia (that is, a relatively global or diffuse impairment of cognitive function as opposed to a well circumscribed focal set of mental impairments) must be present; second, other more distinctive clinical features (referring either to onset or course, or associated neurologic or affective signs) must be present; and third, there must be evidence of cerebrovascular disease which can reasonably be assumed to be related to the dementia (p. 1454-1455).

In discussing Hachinski's research when the Ischemic Score (IS) was introduced, Liston and La Rue make the following observations. Hachinski's research with 24 subjects yielded a bimodal distribution on the IS with 10

subjects scoring 7 or greater and 14 scoring 4 or lower. MID cases were "presumptively identified" by the higher scores, and those cases were found to have significantly reduced mean hemispheric blood flow compared to controls. DAT patients, those scoring 4 or lower, had no significant reductions in cerebral blood flow. Hachinski et al. (cited in Liston & La Rue, 1983a) found a significant correlation of mean hemispheric flow in gray matter with the Information-Memory-Concentration test (IMC), but not with the Dementia Scale (DS). Liston and La Rue note, however, that the IMC depends solely on verbal responses; hence, performance on the test could be adversely affected by brain lesions that impair verbal communication, either expressive or receptive.

Liston and La Rue reviewed a number of other studies using the IS (Harrison et al.; Loeb; & Wikkelso cited in Liston & La Rue, 1983a) They found that the study by Harrison et al. other diagnosis of MID patients "generally failed to correlate significantly with the IS to validate its practical clinical usefulness" (p.1458). Of the Loeb study, they found the "clinical diagnosis is corroborated by the IS in only 52% of the DAT patients and 55% of MID patients," and that "even some of the most discriminating features, i.e., abrupt onset, history of stroke, and focal symptoms, were observed in only 50% of the MID cases" (p. 1459). With regard to the Wikkelso et al. study which concluded that the IS "correlated well with the clinical signs of diffuse arteriosclerotic encephalopathy", Liston and La Rue point out that "since there was no pathological verification of clinical diagnosis, this conclusion is tautological, inasmuch as most of the IS items are by definition clinical features of cerebrovascular disease" (p. 1459).

A number of studies using the WAIS in the attempt to discriminate between DAT and MID, were also examined in Liston and La Rue's review. Those studies were Ladurner et al., 1982; Perez et al. 1975; and Perez et al., 1976 (all cited in Liston & La Rue 1983a) Liston and La Rue found difficulties with methodology and no pathological confirmation of presumed DAT or MID in all those studies, and concluded that the studies failed to demonstrate how the WAIS might "profitably be used to distinguish among subtypes of dementia" (Liston & La Rue, 1983a, p. 1463). Gandolfo, Vecchia, Moretti, Brusa, and Scotto (1985) also investigated the WAIS in differential diagnosis of DAT and MID and found in a matched group of patients that "the comparison between SDAT and MID for IQ, VIQ, PIQ and Det % [Deterioration Index %]" yielded no

significant differences, and that concluded that "this psychometric test [WAIS] does not have any differential diagnostic value" (p. 47).

Liston and La Rue also reviewed cardiovascular studies and found them similarly lacking. With regard to the cardiovascular studies they comment

> To date, clinical studies of multi-infarct dementia constitute a heterogeneous group of investigations with disparate purposes and procedures. The most salient shortcomings of these studies as a whole is the lack of autopsy confirmation of diagnoses, but a number of other methodological problems are evident as well, most notably, small sample sizes, incomplete description of sample characteristics, nonblind assessment and rating procedures, imprecise definition of terms, and insufficient statistical analysis. Moreover, many investigators have failed to document the presence or extent of dementia in their samples before preceding to examine subgroupings based on other clinical or laboratory features (Liston & La Rue, 1983a, p. 1464).

Liston and La Rue conclude: "The collective outcome of this set of investigations raises doubts about the discriminate validity of features commonly used in diagnosing MID and is far from encouraging with regard to ancillary procedures which might be used to verify a clinical diagnostic impression" (p. 1464).

In a second review Liston and La Rue (1983b) examined clinical differentiation of DAT and MID through review of pathological studies. They state

> the question is whether there exists an established set of clinical features that can be practically applied *antemortem* to distinguish PPD [primary degenerative dementia] and MID in a valid and reliable fashion. Careful scrutiny of the literature indicates that this question, at least at present, must be answered in the negative. Studies reported to date present inconsistent and often contradictory findings; even those involving pathological correlational approaches have not provided clear answers. Neither is there certainty about the pathogenesis of cerebrovascular lesions which cause dementia, nor about the size, number, and location that are necessary for these to produce dementia,

whether acting alone or adjunctively with primary parenchymatous degeneration (Liston & La Rue, 1983b, p. 1481).

In this review they do, however, report a study by Rosen, Terry, Fuld, Katzman and Peck (cited in Liston & La Rue 1983b) that "narrow down" to a tentative validation of the correlation of vascular dementia with just five features of the IS: abrupt onset, stepwise deterioration, history of stroke, focal neurological symptoms, and focal neurological signs. Those five features may be compared with those found by Möslä, Paljärvi, Rinne, Rinne, and Säkö (1985) regarding features of IS that show significant correlations with MID described next.

Mölsä et al. (1985) examined the validity of clinical diagnosis in dementia in a prospective clinicopathological study. IS was used and analyzed for its contribution in conjunction with a relatively limited neuropsychological battery: questionnaire, paired-association test, building block test, cube test and digit span from WAIS, and Luria's test of comprehension. Mölsä et al. comment with regard to their results: "AD and multi-infarct dementia were moderately well diagnosed by the clinician (sensitivities and specificities over 70%), whereas only one out of six combined cases [both DAT and MID] was correctly identified" (p. 1087). They comment that there was a "notable trend" of overdiagnosis of multi-infarct dementia. The mean Ischemic Score for AD group was 2.9 and 8.2 for the MID group, a significant difference at $p < 0.001$. The combined group had a mean IS of 4.5 which was not significantly different from either the DAT or MID group. Six items of the 13 on the IS were significantly more common among MID: stepwise deterioration, fluctuating course, relative preservation of personality, emotional incontinence, history of strokes, and focal neurological symptoms. Nonsignificant items of the IS scale were abrupt onset, nocturnal confusion, depression, somatic complaints, history of hypertension, evidence of associated atherosclerosis, and focal neurological signs. The IS was 64.4% successful in classifying patients into three groups, AD, MID and combined.

The efficacy of the IS in discriminating DAT and MID was also investigated by Wade et al. (1987). They examined 65 patients with moderate to severe dementia who had been studied longitudinally during life and

compared clinical and pathologic diagnosis. The Ischemia Scale score sensitivity of diagnosis for DAT without any other diagnosis was 87% and specificity was 78%, but it did not discriminate well between patients with pure MID and those with both DAT and MID. Wade et al. conclude that "The present study shows that the diagnosis of DAT can be made with *some confidence* [italics added] in elderly patients with moderate to severe disease." and "there is nothing in our data suggests that the IS can be used to differentiate MID from mixed dementia." (p. 25)

Leuko-araiosis is present in both DAT and vascular dementias as well as aged normal individuals. Kobari, Meyer, and Ichijo (1990) examined leuko-araiosis in elderly normals, DAT and MID patients. Their study found leuko-araiosis in 21.6% normal volunteers, 52.2% of MID patients, and 61.5% of DAT patients. They noted, however, that the DAT group included more severe cases of dementia than did MID group. The difference in frequency of leuko-araiosis in DAT and MID not significant in Chi-square analysis.

Barr, Benedict, Tune and Brandt (1992) undertook a study to determine whether cognitive test performance alone could distinguish patients with DAT from vascular dementia (VD). In preparing their study Barr et al. reviewed a number of studies using the IS and concluded "A valid and cost-effective way of discriminating VD from AD is still needed in order to more adequately diagnose, and hence manage, patients with dementia" (p. 620). They used discriminant function analysis of neuropsychological test scores in an attempt to differentiate AD from VD.

Results of the discriminant function analysis showed that AD patients performed slightly more poorly on every neuropsychological measure, but when the Bonferroni correction was applied, only BNT and the learning and response bias measures of the Hopkins Verbal Learning Test (HVLT)(Brandt cited in Barr et al.) "came close to significance ($p < 0.0036$)" (p. 624). VD patients had an intact learning curve and retained more words only on trial 3 as compared to DAT patients, and absence of a learning effect over trials and the supremacy of recency over primacy characterized AD patients in their study. AD patients also demonstrated a significantly greater tendency to produce false positives for semantically related distractors. Barr et al. suggest that result may have been obtained because semantic knowledge may be more

impaired in AD patients than in VD patients. They found that response bias for semantically-related distractors was uncorrelated with both verbal learning and verbal fluency. Barr et al. suggest that this may reflect a failure of an aspect to executive control rather than memory *per se*. Classification accuracy in their study was 77%. Barr et al. suggest that accuracy rate argues against the use of a cognitive battery in isolation, but that the neuropsychological battery may be helpful in the context of a comprehensive neuropsychiatric examination.

Budzenski (1986) in her doctoral dissertation used discriminant function analysis to identify those variables which best discriminated between SDAT and a combined MID/PD groups. She found memory variables of interference and intrusions, the semantic memory variables of verbal fluency and confrontation naming, and the recognition variable were found to discriminate best between the groups and to best identify SDAT.

Parlato, Carlomagno, Merla, and Bonavita (1988) also found verbal function variables useful in discrimination DAT and MID patients. They examined patterns of verbal memory impairment in dementia. Parlato et al. matched the AD and MID patients for degree of severity and included a normal group (NC) of similar age. Their primary instrument was Rey's Auditory-Verbal Learning Test. They found that both DAT and MID patients were significantly different than normal controls ($p < 0.001$) on the sum of items recalled after five trials (immediate memory) and delayed recall (15 min). The DAT group was worse than the MID group ($p < 0.01$). The groups differed on learning effect in the following ways: NC showed a significant increase on each subsequent trial with the exception that no difference was found between the fourth and fifth trials; DAT patients showed a significant increase only between the first and second trials; MID showed a significant increase between first and second trial and between the third and fourth trial. Parlato et al comment that "the general impression was that MID patients, whatever their memory deficit, retained some learning effect which was not true for AD patients" (p. 347).

In examining delayed recall, Parlato et al. (1988) found that DAT patients did not retain the small increase they showed in immediate trials; first recall and delayed recall did not differ. On delayed recall, the MID

group, like the NC group, demonstrated intermediate delayed recall with performance between the first and fifth immediate recall. Examination of recall as function of serial position revealed that DAT performance was worse than MID performance in positions 1-5 and 6-10 but not in positions 11-15. In contrast, for both NC and MID serial position effect was due to performance on items 1-5 and 11-15 which was significantly better than performance on items 6-10. Other memory parameters examined--immediate visual memory and digit span--did not differ between SDAT and MID.

On the basis of their findings Parlato et al. concluded that the "verbal memory deficit in AD patients is more marked than in MID when the two groups are matched for general cognitive impairment" (p. 346). For MID, learning effect and serial position effect showed a normal pattern while with DAT learning effect was negligible and serial position effect demonstrated a "peculiar pattern", i.e., worse than MID on positions 1-5 and 6-10, but similar to MID on positions 11-15. In a preliminary discriminant function analysis by immediate and delayed memory score, "the learning effect and the serial position effect gave 58 to 76% correct classification into MID and AD categories for each separate parameter" (p. 349-350).

Patterns of language impairment in DAT and MID were also examined by Kontiola, Laaksonen, Sulkava and Erkinjuntti (1990). Their subjects were careful matched for degree of impairment as well as on other variables, age, sex, and education. They note that other studies suggest that the language disorder in DAT is primarily receptive, characterized by semantic and syntactic disorders, while expressive speech is fluent and better preserved. In MID, language impairment is primarily expressive and includes grammatical simplification and restriction of lexical choice. Nominal dysphasia and impaired word fluency are present in both disorders.

In their study, Kontiola et al. found that MID patients were significantly better on measures of understanding temporal relationships, understanding complex grammatical structures, repetition of sentences, repetition of dissociative sentences, and repetition of a story. AD patients showed their greatest difficulties in understanding and constructing complex grammatical structures. They report that the MID group was mostly impaired in simple and basic language abilities, such as recognition of words, naming, and repetition. They interpret these findings as suggesting that in MID the

"degenerative changes in the central nervous system seem to affect especially the complex forms of language without disturbance in the symbolic aspects of language and the disorders lie primarily in the receptive speech" (p. 378).

Taking a different approach, Bucht, Adolfsson, Winblad (1984) compared DAT and MID with approximately the same degree of dementia and same duration of illness with controls on a number of laboratory and other variables. They found that the MID patients were significantly older. Sixty-three percent of the DAT patients were free of other disease while 65% of the MID group had cardiovascular disease. Five percent of DAT and 30% of MID patients had previous depression. Six percent of DAT patients had focal neurological signs compared with 70% of the MID group. ECG recordings were normal for all DAT patients, but abnormal for 75% of the MID group, while EEG yielded generalized slow frequencies for 79% DAT and 65% MID. CT scans showed significantly greater ventricular dilation in MID, but cortical atrophy did not differ significantly among DAT, MID and normal groups. Homovanillic acid (HVA) in DAT patients was significantly lower than controls and lower, but not significantly so, than MID. A potential weakness in this study is that the patient groups were classified primarily on the basis of the IS and it finds that the patients so classified exhibit the characteristics by which they were classified.

Cummings, Miller, Hill, and Neshkes (1987) examined neuropsychiatric aspects of MID and DAT. They found no differences in frequency of delusions between DAT and MID, and the content of delusions where they did occur were similar--simple paranoid beliefs. Seventeen percent of patients with DAT had depressive symptoms, but none had severe depression, while approximately 27% of MID (4/15) exhibited major depressive episodes and 60% manifested depressive symptoms. Hallucinations occurred in both groups but were not frequent, e.g., one patient (1/15) with MID and one (1/30) with DAT had auditory hallucinations and three MID patients had visual hallucinations.

Barclay, Zemcov, Blass, and Sansome (1985) investigated survival rates in DAT and vascular dementias and found that "survival in DAT was consistently better than in vascular dementia whether measured from date of evaluation or estimated date of onset,"and that "from date of evaluation, 50% survival was 3.4 years for DAT compared with 2.6 years for MID and 2.5 years for MIX [individuals with features of both DAT and MID]" (p. 836). Three years after

diagnosis, survival in DAT was 88% compared to 66% in MID and 58% in MIX" (p. 837). Male-to-female ratio in series was 1:2 in DAT and 1:1 in MID. Rate of progression of impairment, however, did not differ between DAT and MID.

Binswanger Type Dementia

It is difficult to place Binswanger type dementia in this review for while it is a vascular dementia, it is also a subcortical dementia. Binswanger type dementia differs from the other subcortical dementias to be examined in that it does not selectively involve the basal ganglia. Román (1987) reports that while 50% of dementia in United States is attribute to AD, in Japan 53% of patients with senile dementia have a dementia of vascular origin. He indicates that Binswanger's disease which was until recently rarely reported in North America is being recognized with increasing frequency with the advent of high-resolution CT and MRI. He says of his review:

> This review of recent clinical, radiologic, and neuropathic studies underlines the fact that ischemia affecting the periventricular white matter may cause the disconnection of a relatively intact cerebral cortex, resulting in a true subcortical dementia. The relevance of this mechanism appears to have been largely overlooked previously. The name *senile dementia of the Binswanger type* (SDBT) is suggested for this vascular form of dementia" (Román, 1987, p. 1782).

and describes the disorder as follows:

> The SDBT is a progressive dementia of slow onset and insidious progression, usually accompanied by manifestations of pseudobulbar palsy, emotional incontinence, lateralized motor signs, corticospinal or corticobulbar tract dysfunction and gait difficulties. Small-step gait (*marche à petits pas*) and gait apraxia are typical, and frequent falls are an early sign. Urinary urgency or incontinence occurs early in the disease. In contrast these features are late occurrences in AD (p. 1784).

Roman reports, further, that frontal lobe signs (personality change; loss of incentive, drive, and insight; apathy; and profound abulia) are common. Forgetfulness and mild confusion occur in early symptomatic forms and an amnestic syndrome may dominate at the onset of the illness. Aphasia,

hemianopsia, anosognósia and parietal neglect are rarely seen. Clinically Binswanger type dementia is a subcortical dementia and is different than MID which is considered a cortical dementia.

While Román does not emphasis the point, the presentation of BD is in many respects similar to the early presentation of AD. While motor signs do not appear early in the course of AD, all of forgetfulness, confusion, "an amnestic syndrome", loss of drive and incentive, personality change, emotional lability, aphasic symptoms, and insidious progression do occur early in the course of AD. Further, the high resolution CT or MRI equipment required to detect SDBT are not readily available to many clinicians. Together, these factors may make the differential diagnosis of SDAT and SDBT one of the most difficult diagnostic questions for clinicians.

DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE AND SUBCORTICAL DEMENTIAS

Subcortical Dementia--General

Huber and Paulson (1985) explain the concept of subcortical dementia and differentiate it from cortical dementias. They argue that subcortical dementia affords a unique opportunity to study progressive memory loss associated with dementia because in contrast to cortical dementias, like AD, it does not involve dysfunction of language (aphasia) and perception (agnosia and apraxia). They note that progressive dementias are "traditionally associated" with neurological disorders that produce major degeneration of the cerebral cortex, and that "recently dementia has been recognized as an integral part of neurologic disorders in which the primary degeneration involves subcortical structures such as the basal ganglia and brain stem" (p. 1312). The concept of subcortical dementia includes supranuclear palsy, Huntington's disease, and Parkinson's disease, with Wilson's disease, traumatic head injury, and multiple sclerosis as other possible examples.

In contrasting AD and subcortical dementia, Huber and Paulson observe that in AD initial symptoms usually involve memory which deteriorates steadily throughout the course of the disease, the loss of higher order associative functions, and impairment of both expressive and comprehensive language. Other related disorders may include perceptual misinterpretations and deficits in perceptual motor-activity. Areas primarily affected in AD include the frontal lobes, the association cortices, and the hippocampal gyri. In

subcortical dementia the predominant features include slowing of mental operations and progressive impairment of memory. Cognitive changes may resemble those of cortical dementias except for relative preservation of higher-order associative functioning. Subcortical dementia is likely to be associated with aphasia, agnosia, or apraxia, and subcortical dementia may progress more slowly than cortical dementias. Each of the subcortical dementias is associated with a distinct movement disorder.

Parkinson's Disease

This review will focus on Parkinson's disease as it is the subcortical disorder that is most frequently seen, and the nature of the cognitive deficits presents important diagnostic issues. Huber and Paulson (1985) state that the relationship between Parkinson's disease (PD) and dementia is not well understood. They consider, following Liberman 1979 (cited in Huber and Paulson), that Parkinson's disease with and without dementia may represent two different disorders and point out that Parkinson's disease with dementia has a later age of onset and a shorter and more progressive course. PD with dementia responds less well to L-Dopa, is characterized by more generalized involvement, and does not correlate well with local neuronal loss while severity of the benign form correlates well with neuronal loss within the substantia nigra. Pathology studies, by their report, yield contradictory findings. Some reports provide an "indistinguishable pattern of degeneration with plaques and tangles in the hippocampal area and similar degrees of cortical cell loss" while others "have suggested that dementia in Parkinson's disease results primarily from subcortical degeneration because of the paucity of higher-order dysfunction, such as aphasia, agnosia and apraxia" (Huber & Paulson, 1985, p. 1314). They consider that damage to the basal ganglia in PD prevents information from being conveyed to the frontal lobes such that PD patients resemble patients with frontal lobe damage except for difference related to associative functions and note that PD patient's performance on the Wisconsin Card Sorting Test resembles the performance of persons with frontal lobe disorders, that is, they solve fewer problems and tend to perseverate.

A group of Finnish researchers, Helkala, Laulumaa, Soininen, and Riekkinen (1989) examined different error patterns of episodic and semantic memory in AD and idiopathic PD with dementia and compared those patients with

normal controls (NC). Memory examined with story recall tests, list learning tests with Buschke selective reminding and category naming test. Helkala et al. found that on story recall tests both patient groups differed significantly from NC. PD and AD groups did not differ in immediate recall or recall after interference on the Luria memory test. With the Luria memory test, two fairy tales are told to patients sequentially, and after recall of second story, patients are asked to recall as much of the first story as they can; following free recall, probe questions are asked. While the AD and PD did not differ significantly on immediate recall, PD patients produced significantly more items after 30 minute delay. PD patients also recalled significantly more story items immediately and after 1 minute delay, but when scores for story recall without probe questions were compared, PD patients did not recall more items in the immediate recall test than the AD patients. With one-way analysis of variance Helkala et al. found significant group effect of the stories recalled after probe questions in immediate recall and an "almost significant" group effect on story recall after a one-minute delay. Group comparisons demonstrated that the PD patients recalled significantly more probed items in the immediate and delayed recall part of the Luria memory test.

Analysis of the list learning test administered by Helkala et al. failed to reveal significant difference between AD and PD group for retrieval from immediate and long-term memory, but on recognition, PD patients recognized significantly more words than AD though significantly fewer words than NC. There was no difference between AD and PD patients on category naming. Helkala et al. did, however, find a difference in error types between the patient groups. PD and AD patients did not differ on prior-story intrusions, but the AD group had more significantly more extra-story and extra list intrusions than PD; neither group perseverated significantly more on the category naming test than did normal controls, but there was significant difference between PD and AD patients in that the PD group perseverated less than AD. The AD group affirmed significantly more false positives on recognition than the PD group. Helkala et al. (1989) concluded that "AD patients perform poorly because of their inability to inhibit irrelevant information and increased sensitivity to interference, whereas the deficits of PD patients solely reflect a sensitivity

to proactive interference of perseveration, but not, however, an inability to inhibit irrelevant information" (p. 1247).

Heindel, Salmon, Shults, Walicke, and Butters (1989) compared multiple implicit memory systems in AD, HD (Huntington's disease), and PD. Their findings revealed that HD patients were impaired on pursuit-rotor and performed normally on verbal priming tasks while DAT patients performance was not significantly impaired relative to normal elderly controls on the pursuit-rotor task, but were impaired on the lexical priming task. Heindel et al. point out that since HD and AD did not differ significantly on DRS scores, the differences obtained cannot be attributed to the severity of dementia. Demented PD patients were impaired on two tests of implicit memory, unlike the HD and AD patients. The demented PD patients, who evidenced less overall dementia, performed better on recognition memory than did the HD and AD groups. Like the HD patients, PD patients' deficits on motor skill learning was correlated with degree of dementia but not with motor symptoms. While demented and nondemented PD did not differ in severity of motor symptoms, only demented PD patients were impaired in learning pursuit rotor skill.

Mohr, Litvan, Williams, Fedio and Chase (1990) argue that there are differences in the cognitive profiles in AD and PD groups with equivalent degrees of overall intellectual impairment. "Overall" intellectual impairment of dysfunction meant, in this case, that IQ scores were not significantly different. However, the AD group's mean WMS Memory Quotient was 18 points lower PD group's--76 ± 2.8 versus 94 ± 6.4, respectively, and whether patients who differ that greatly can be considered to have "equivalent degrees of overall intellectual dysfunction" is debatable. On the basis of their findings they concluded that "Visuospatial tasks not principally associated with memory, evidenced some differentiation between the two demented groups. Object Assembly (OA), a visuospatially mediated task necessitating the ability to abstract from an incomplete stimulus and visuospatial reasoning, both skills which have been associated with frontal function, was significantly impaired in the Parkinsonian compared to controls as well as to Alzheimer's patients" (p. 294). This appears to be a relatively weak study. While findings are in line with other research showing visuospatial deficits in PD, they do not consider that OA is the least reliable of the WAIS-R subtests and that small raw score differences can likely be accounted for in terms of

subtest's reliability, and small numbers--11 in each group--are not likely to be stable.

In a stronger study, Sahakian et al. (1988) investigated visuospatial memory and learning in DAT and PD. Computerized tests of different aspects of visual memory, complementary tests of visual pattern recognition, match-to-sample and visuospatial recognition, were employed. PD patients were divided into two groups; (1) those newly diagnosed and not receiving medication (NMED PD) and (2) those later in the course of their disease and receiving medication (MED PD). DAT patients were mildly impaired.

Sahakian et al. found that on the simultaneous match-to-sample, the DAT group exhibited similar choice accuracy to the control group, but both PD groups were significantly impaired. On the Delayed match-to-sample task, the DAT group's choices approached chance while controls showed little decrement in performance The two PD groups yielded different patterns of performance. MED PD patients showed significant decline in performance irrespective of delay, while NMED PD exhibited a qualitative similar but not significant decline in performance.

The conditional visuospatial associative learning and delayed response tasks used by Sahakian et al. proved almost too difficult for DAT patients who had difficulty reaching criterion. DAT patients were severely impaired in acquisition of conditional visuospatial discrimination. Mean errors for the DAT patients were 47.8 as compared with 5.8 for controls. MED PD patients were also significantly impaired relative to controls. The NMED PD group was significantly reduced in their attainment of criteria but none of the other differences were significant. On the delayed response task first trial scores, DAT patients were significantly impaired relative to their controls as were the MED PD groups, but NMED PD showed no significant impairment.

Tactile discrimination learning deficits in AD and PD were investigated by Freedman and Oscar-Berman (1987). They expected to find greater deficits in AD because that disease has been demonstrated to involve the parietal cortex early in the course of the disease and because parietal lesions in nonhuman primates impair tactile learning. PD is, conversely, demonstrated to be a disorder of the basal ganglion and brain stem. Freedman and Oscar-Berman found that learning of a novel tactile discrimination problem was, as they predicted, significantly impaired in DAT patients as compared with patients

with idiopathic Parkinson's disease and dementia when both groups are equated for severity of cognitive impairment.

DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE AND DEPRESSION

Hart, Kwentus, Wade, and Hamer (1987) assert that the "Differential diagnosis of dementia of the Alzheimer's type (DAT) and affective disorder can be so difficult that 5%-15% of patients with a presumed diagnosis of dementia will be found at follow-up to have only an affective illness . . . Discriminating the cognitive impairment attributable to early DAT from that attributable to depression can be particularly difficult" (p. 236). Terry and Katzman (1983) report that

> In several recent clinical series it has been reported that about 10% of patients referred with an initial diagnosis of dementia are found on evaluation to have a pseudodementing functional illness, in most cases psychological depression . . . Depression can be mistaken for dementia because of an inadequate mental status examination . . ., but some older depressed individuals have a true cognitive impairment that is reversible when the depression is treated, a condition referred to as 'dementia in depression'. Such patients often have a history of a significant depressive episode, a relatively moderate degree of memory loss, and a tendency to plateau (p. 499).

Hart et al. (1987) observe that memory loss complicates differential diagnosis of DAT and *pseudodementia* because although memory loss and other cognitive declines are early symptoms of DAT, those same deficits are also a common feature of some psychiatric illness, especially depression. And while memory complaints are often subjective in depressed patients, moderately depressed patients are impaired on psychometric tests of memory. Further, early DAT victims deny memory change and are often able to mask the intellectual deterioration, but present with "depressed mood, anxiety, loss of interest, decreased spontaneity, somatic complaints, and irritability" (p. 101) that can cause a patient with early DAT to appear to be suffering from an affective disorder.

In considering the differential diagnosis of dementia and depression, Hagberg and Larson (1985) remark that "quantitative analysis does not give

enough information when differing depressives from dementia. Therefore a qualitative analysis of performance should be added" (p. 328). They observe that perseveration can be readily seen in dementia of a frontal type (DFT), rotation is more frequent in DAT and sometimes in MID, but those qualities are not found in pseudodementia. A lack of systemic solution and of self-criticism is frequently found in DFT or Pick dementia but less so in depression.

DesRosiers (1992) reports that depressed patients with CNS symptoms can account for 5% of admissions to neurological units and that depression is diagnosed in up to 20% of organic patients, including those suspected of early DAT. Further, nearly 60% of patients thought to exhibit depressive dementia developed a frank primary dementia within three years (Alexopoulos; Kral & Emery cited in desRosiers 1992).

In examining the differential diagnosis of DAT and depression, desRosiers reviewed and offered comments on a 1979 "landmark paper" by Wells (cited in desRosiers, 1992). Wells summarized the 'major clinical features differentiating pseudodementia from dementia' in tabular form. DesRosiers reproduced that table with his own additions--asterisks in the right margin identifying items for which the evidence is equivocal when early Alzheimer's disease is the alternative diagnosis. That table is presented here as Table 4.1. The issues for which desRosiers believed the evidence is equivocal are reviewed here.

With regard to *Clinical Course and History*, desRosiers states that one of the most debated items in Wells' table is that a history of previous psychiatric episodes is more prominent in patients with pseudodementia, but desRosiers reports that recent surveys (Agbayewa; Rovner et al.; Burns et al. cited in desRosiers, 1992) have all found that previous depressive illness is also increased in AD patients. DesRosiers suggests that Wells' observations regarding *Onset* are equivocal. He describes a prospective study (Zubenko cited in desRosiers, 1992) that compared 84 AD patients and 40 MID patients and found that a "punctuated progression of illness was just as likely in either group" and that "AD patients who were also depressed were least likely to show an insidious progression" (p. 631). DesRosiers cautions, however, that these observations do not necessarily mean that the onset was not

Table 4.1

Wells' (1979) Major Clinical Features Differentiating Pseudodementia from Dementia with desRosiers' Additions

Clinical features	Pseudodementia	Dementia
Clinical course and history		
Family is aware of dysfunction and severity	Usually	Rarely*
Onset can be dated with some precision	Usually	Rarely*
Duration of symptoms before physician is consulted	Short	Long*
Progression of symptoms	Rapid	Slow*
History of previous psychiatric illness	Usual	Unusual*
Complaints and clinical behaviour		
Nature of complaints	Cognitive*	General*
Quality of complaints	Detailed	Vague*
Shortcomings	Emphasized	Concealed
Accomplishments	Downgraded	Valued
Coping strategies (eg diaries)	Minimal	Adequate
Emotional Reaction	Distress	Unconcern*
Depressive affect	Pervasive	Shallow*
Social skills deterioration	Early	Late
Behavioural and cognitive congruency	Inconsistent	Consistent
Nocturnal confusion	Absent	Present
Cognitive and intellectual functions		
Attention	Preserved*	Impaired*
Concentration	Adequate	Deficient
Answers to questions	Don't know	Near miss*
Recent and remote memory equally impaired	Usual*	Unusual
Memory gaps	Frequent	Infrequent
Performance on tasks of similar difficulty	Variable	Consistent

(desRosiers, 1992, p. 631)

insidious in AD but, rather, that the patients were often brought to medical attention following a concurrent illness or some social trauma. The difficulty lies not so much in whether the onset was insidious but in the accuracy of reporting and observation by the caregiver.

DesRosiers expresses further reservations regarding *Complaints and clinical behaviour*, and comments that Wells observed that patients with

depressive dementia could be expected to show a pervasive change in affect with distress and hopelessness as the dominant symptoms while AD patients often seemed unconcerned and their affect manifested as labile and shallow. DesRosiers argues that recent research (Reifer et al; Zubenko & Moossy cited in desRosiers, 1992) has shown that many AD patients can be given a secondary diagnosis of major depression following standard assessment manuals. He suggests that part of the difference between Wells' observations and those of later researchers may arise because of the "debate whether the major depression in primary dementia conforms to the syndromes diagnosed in depressed elderly, cognitively impaired or not" (p. 631). Observations of other observers (Greenwald et al.; Merrian et al.; Beck cited in desRosiers, 1992) essentially conform to those of Wells.

The nature of *Complaints* in DAT and depression is examined. According to desRosiers comments by clinicians and a recent study (Feehan et al. cited in desRosiers) support Wells' 1979 position that AD patient complained less about their memory and other cognitive difficulties than warranted while depressives did the contrary. It appears that elderly depressives memory concerns arise primarily from their inability to manage the attentional skills that are necessary for learning, but not from retention difficulties *per se*, and they endorsed items concerning all of attention, concentration, and recall while anmesics tended to endorse primarily items concerning recall and not attention or concentration. DesRosiers suggests the divergence of complaints and performance may provide a means of dissociating depressives and dements on standardized tests.

DesRosiers' comments regarding *Cognitive features* focus attention and concentration, 'don't know answers', and recent versus remote memory lapses. With regard to *Attention and concentration*, he reports that depressives do not encode as much as healthy controls and often not much better than mild AD patients, but depressives will retain as well as controls that which they manage to register on tasks like story recall. Digit span forward shows little difference between normals and mild AD, but digits backward yields greater differences with normals better. Studies comparing AD and organically normal persons when both are depressed are, according to desRosiers, still needed. He reports concerning *Don't know answers*, that studies with the

orientation section of the MMSE show that, contrary to Wells' initial observations, AD patients gave more "I don't know" answers than depressives (Young cited in desRosiers, 1992), but that reply was dependent upon factors like the type of question asked, the respondent's behavioural style, social class, and education. The actual differences in number of "I don't know" responses were small and the standard deviation in depressives was almost twice the mean. Regarding *Recent vs remote memory lapses*, desRosiers reports that on standardized measures covering public events and figures from the past, "depressed patients show a temporal gradient over the decades tested akin to that seen in healthy elderly" (p. 633), but, desRosiers suggest, the question of whether primary dementia affects recent memory more than remote memory is still controversial.

In concluding, desRosiers (1992) observes "The above review of Wells' proposed discriminating features suggests some attributes (eg personal vs instrumental competence, complaint vs performance) might provide valuable pointers of the conditions where as others (eg history of depression remain more controversial" and "The greatest obstacle at this stage is that practically none of the proposed discriminating features in Well's nomenclature have been validated through prospective studies" (p. 634-635).

Fopma-Loy (1986) draws essentially from Well's observations but develops the difference between depressives and AD patients' perception of and attitude toward their cognitive losses. She reports the primary complaint in pseudodementia is of failing memory, and that those individuals will often precisely recount instances in which memory losses occurred as a means of emphasizing to the examiner the severity of the memory losses. The demented patient, in contrast, may be unaware of readily observable deficits or, if he or she is aware, will often attempt to conceal the cognitive losses by relying on notes and other aids.

In reviewing a study by Whitehead (1973, cited in La Rue, 1982), La Rue notes that the "performance of ill depressed patients exceeded that of dementia patients on all memory tasks, with the exception of Digits Forward" (p. 98). On other measures, the pattern of errors was useful in differentiating depressed from dementia patients. According to La Rue, Paired-associate learning most clearly illustrated the difference in error

patterns. While omission errors were common in both groups, depressed patients made more transposition errors--misparing of stimulus and response words, dementia patients produced more random errors--the intrusion of words never presented. He suggests that the frequency of omission errors is not diagnostic, but the distribution of transposition versus random errors can be used to differentiate the groups. Another study (Miller & Lewis cited in La Rue, 1982) examined recognition memory for geometric designs by a continuous recognition procedure. That study found that, as a group, dementia patients were less accurate in their recognition of repeated designs than the depressed group, and that they also had much higher rates of false-positive recognitions. The depressed patients exhibited, contrariwise, an extremely cautious response style that yielded lower rates of false positives and somewhat lower rates of correct recognition than that of normal subjects. La Rue concludes

> The distinctive signs in memory performance of patients with depressive pseudodementia include: (1) mild to moderate impairment in the acquisition and recall of new information--that is, performance is impaired relative to appropriate age norms, but impairment is generally not severe enough to induce complete disorientation to place or time; and (2) a pattern of errors characterized by "don't knows" and near misses, without significant confabulations or intrusions of irrelevant information (p. 99).

Hart, Kwentus, Wade and Hamer (1987) investigated incidental memory in 15 DAT patients, 15 depressed patients, and 19 normals. They hypothesized that "the depressed patient's incidental memory for rehearsed digit-symbol items would be minimally affected by attentional and motivational deficits and that this measure would therefore be helpful in discriminating patient groups" (p. 236). They administered the Digit-Symbol subtest of the WAIS but instructed the subjects to complete every item, then immediately thereafter presented the subjects with a sheet with the nine Digit-Symbol test boxes, minus the symbols. Their subjects were instructed to recall the symbols and place them in the boxes below the appropriate number. Hart, Kwentus, Wade, et al., recorded the number of items completed in 90 seconds, the total time for test completion, the number of symbols matched to number, and the total number

of symbols recalled whether or not they were correctly matched. They found the following significant at least $p < 0.5$:

> (a) mild DAT and depressed groups performed more slowly than control subjects in completing digit-symbol items but did not differ from one another, (b) depressed patients recalled more digit-symbol pairs and total symbols than DAT patients, and (c) depressed patients recalled fewer digit-symbol pairs than normal control subjects but a similar number of total symbols
>
> (Hart, Kwentus, Wade et al. 1987, p. 237).

In another paper Hart, Kwentus, Taylor, and Harkins (1987) hypothesized that motivational and attentional deficits in depressed patients would have maximum impact on learning efficiency rather than on the retention of well learned material, and that depressed patients would show essentially normal memory consolidation while patients with mild DAT would fail to consolidate information effectively and would forget it rapidly. They employed a visual recognition paradigm (Rate of Forgetting Test) as well as other tests and adjusted stimulus exposure times to equate learning in mild DAT, depressed patients, and normal controls. Their analysis demonstrated that there was no significant difference in the performance of mild DAT and depressed patients on tests of general intelligence, reasoning, verbal fluency, and concentration, and that neither group was impaired on relatively simple tests of right-left discrimination, graphomotor construction, and judgment of pictorial incongruities. The DAT patients were, however, impaired compared to both depressed patients and normal controls on measures of temporal orientation and verbal memory. On the Rate of Forgetting Test, recognition was examined at 10 minutes, 2 hours and 48 hours. They found:

> (a) depressed and DAT patients, as expected, did not differ from normal subjects on the criterion test and (b) depressed patients and normal subjects had a higher mean percentage correct at 10 min, 2 hr, and 48 hr relative to DAT patients and did not differ from one another. Univariate tests within each group also revealed that (a) only DAT patients demonstrated forgetting by 10 min ($p < .0001$), (b) all three groups demonstrated forgetting from 10 min to 2 hr ($ps < .001$, and (c)

both depressed and normal subjects demonstrated forgetting from 2 hr to 48 hr ($ps < .0001$) (Hart, Kwentus, Taylor, et al. 1987, p. 102).

In discussing their results Hart, Kwentus, Wade et al. comment that "no single measure could be expected to completely differentiate DAT and depressed patients, but there was less overlap in forgetting rates [on the visual recognition measures for DAT patients and depressed patients] than in scores on Wechsler Memory Scale Logical Memory and Visual Reproduction subtests" (p. 104), and point out that on the Wechsler subtests 20%-40% of the depressed subjects scored below the mean of the DAT group, and that 60% fell within one standard deviation of the DAT mean.

DIFFERENTIAL DIAGNOSIS OF VERY MILD ALZHEIMER'S DEMENTIA AND NORMAL AGEING

The introduction to this investigation emphasised the importance of the early diagnosis of DAT if that disorder is to be treated successfully. It is essential, then, to differentiate changes in memory function in DAT from those which occur in normal ageing.

Dawe, Procter, and Philpot (1992) reviewed concepts of mild memory impairment in the elderly and their relationship to dementia. They begin with the concept of benign senescent forgetfulness (BSF) introduced by Kral (cited in Dawe, Procter, & Philpot, 1992). Kral described individuals who, despite poor recall of an event on demand, could recall the event itself. Those individuals were aware of their memory difficulties and would attempt to compensate for them. Further, they were usually able to recall the memories later. Kral contrasted those individuals with a 'malignant' form of memory loss. Individuals with the 'malignant' memory loss were characterized by an inability to recall events from the recent past, which lead in turn to disorientation and the retrogressive loss of more remote memories. Individuals with this form of memory loss were unaware of their deficit and confabulated. Kral followed the two groups for at least four years and reported in 1978 (Kral, cited in Dawe, Procter, & Philpot, 1992) that only one of the 20 subjects in the BSF group had show further deterioration while all of those in the malignant groups had done so. In a more recent study (Parnetti et al. cited in Dawe et al. 1992) only one of nine subjects developed dementia over a four-year follow-up period, and in a 1984 study

(Loring et al. cited in Dawe et al. 1992), none of seven individuals with BSF showed further deterioration over one year.

In a three year follow-up of patients with "supposed" benign senescent forgetfulness, O'Brien et al. (1992) found that six out of 68 patients (8.8%) diagnosed as suffering benign senescent forgetfulness had become demented three years later. Although that level of incidence is twice as large as would have been expected in a normal aging population using the highest estimate rate of incidence (Nilsson; Magnusson cited in O'Brien et al. 1992), the number of patients who developed dementia was small and there was no control group. O'Brien et al. comment that "it is clear that although memory complaints in the elderly must be taken seriously and may sometimes indicate early dementia, in the majority of cases a finding of normality remains accurate three years on" (p. 484). O'Brien et al. (1992) also found that there were no clinical features which predicted subsequent dementia. They note that CT scans were abnormal in three of the six cases who subsequently developed dementia, but CT scans were also abnormal in 21/58 (36%) of other non-demented subjects.

Dawe et al. (1992) reviewed the literature on mild memory changes under a number of other labels. "Mild dementia" is a term that has been used in a number of cross-sectional and longitudinal epidemiological studies, but that term is only loosely defined. As used, "the single common feature of mild dementia was the presence of mild cognitive impairment, *presumed to be a decline from a higher level of function*" [italics added] (Dawe et al., 1992, p. 474). 'Mild dementia' is not a diagnosis of itself but a label for the early stage of any one of several neuropathological distinct disorders. Kat et al. (cited in Dawe et al., 1992) identified 20 of 350 individuals over the age 65 as mild dementia. Six of the 20 or 30 percent went on to develop definite dementia within three years.

'Very mild cognitive decline' is part of the Global Deterioration Scale (GDS) (Resiberg et al. cited in Dawe et al., 1992) and is described as the 'phase of forgetfulness' (GDS 2). At that stage the patient typically complains of memory deficit, misplacing things, and forgetting names previously well known to him or her. Memory impairment is not apparent in clinical interview, but the person performs below the mean for his or her age

and his or her own verbal intelligence level on three out of five standardized memory tests. Using this measure Resiberg et al. found two of 40 'community' patients, or 5%, became demented over a 3.5 year period.

'Limited cognitive disturbance' (LCD) derives from the Comprehensive Assessment and Referral Evaluation (CARE; Gurland et al. 1982 cited in Dawe et al. 1992). Limited cognitive disturbance contrasts with pervasive cognitive disturbance or dementia. To be classified as LCD, a patient must meet five criteria:

> The patient must (i) report a decline in memory; (ii) have increased reliance on notes and reminders; (iii) occasionally (less than once a week) forget names of acquaintances, forget appointments or misplace objects; (iv) occasionally (less than once a month) have 'destructive' or 'dangerous' memory lapses such as burning cooking or leaving gas taps on; (v) have one or two errors on cognitive testing, eg 'forgets current or past president, exact dates, phone number, postal code, dates of marriage or move to present habitation or cannot remember interviewer's name even on the third challenge'. These problems should not interfere with activities of everyday living (Dawe et al., 1992, p. 475).

Unfortunately, no follow-up studies of that "diagnosis" are available.

'Age-associated memory impairment' (AAMI) is an attempt by the NIMH Work Group (Crook et al. cited in Dawe et al. 1992) to "operationalize" a definition of an age related memory impairment, but it does not necessarily imply that the disorder is non-progressive, and it is non-specific with regard to etiology. Further, Smith et al. (1991) found, using objective memory criteria for diagnosing AAMI, considerable variation in the rate of classification for subjects as AAMI varied considerably (77% to 96%) depending on the memory assessment battery they received, and rates for individual tests varied from 7% to 96%. They conclude that the criteria for age-related diagnosis of age-associated memory impairment and for late-life forgetfulness (LLF) lack reliability.

'Questionable dementia' is used in the Clinical Dementia Rating (CDR) (Hughes, Berg, Danziger, Coben & Martin, 1982) and is described by Dawe et al. (1992) as

> a 'mild consistent forgetfulness with partial recollection of events' in which the patient is fully oriented, has only doubtful impairment in

> solving problems and only doubtful or mild impairment in what are termed 'community affairs'. Life at home, hobbies and intellectual interests are well maintained or only slightly impaired and the patients remain fully capable of self-care (p. 474).

The Clinical Dementia Rating (CDR)

The Clinical Dementia Rating was developed from a body of research carried out by the Memory and Ageing Project of the University of Washington in St. Louis, Missouri. The CDR is a "staging instrument" and could have been discussed in the section of this dissertation dealing with stages and subtypes of dementia. The CDR is likely a useful instrument for clinical staging, and accurate assessment of the stage of dementia a patient is suffering is important. The findings of a number of papers already reviewed were confounded by the researchers' failure to determine the stage of dementia or degree of dementia their subjects were suffering. The CDR is discussed here because of one rating, CDR 0.5, which identifies 'questionable dementia'. 'Questionable dementia' is similar in its presentation to the other mild cognitive losses described variously as 'benign senescent forgetfulness', 'limited cognitive disturbance', 'mild dementia', 'very mild cognitive decline', and 'age-associated memory impairment'.

In introducing the CDR, Berg (1988) observes "until there is a validated biological marker for AD that does not require brain biopsy or autopsy, clinical investigations of SDAT required a valid, acceptable set of research diagnostic criteria and *a system for staging the disorder as to severity* [italics added] (p. 88). The criteria developed by Berg and his associates in the Memory and Aging Project of Washington University is "consistent with" the diagnosis of "probable Alzheimer's disease" and the diagnosis of primary degenerative dementia by DSM-III criteria. Berg reports that the criteria have been validated by the finding that each of 25 individuals diagnosed as SDAT who have come to autopsy have demonstrated the histologic features of AD.

The essential elements of the CDR are described by Hughes, Berg, Danziger, Coben, and Martin (1982). The CDR begins with the Initial Subject Protocol (ISP), a standardized structured interview in which information is gathered on the subject's family history, social, educational and cultural

background, and medical and psychiatric history from the subject and a collateral source, usually the subject's spouse or child. In addition to providing or confirming the information provided by the subject on the above matters, the collateral source is asked to rate the subject on a number of memory items and some problem solving abilities. The ISP also includes the Dementia Scale (DS), the Short Portable Mental Status Questionnaire (SPMSQ) and the Face-Hand Test (FHT), as well as tasks from the Boston Diagnostic Aphasia Evaluation (BDAE). The subject is also evaluated for depression. All these instruments influence the global CDR but none of them nor any portion of the ISP determine the CDR by direct numerical scoring. The subject is further rated, on the basis of information from the subject and the collateral source, on each of six cognitive and behavioural categories that form the basis of the CDR. Those categories are memory (M), orientation (O), judgment and problem solving (JPS), community affairs (CA), home and hobbies (HH), and personal care (PC). In each of these categories, the subject's function is rated not in relation to the general population, but in relation to his or her own cognitive ability and past performance. Subjects are assigned a rating of CDR 0 (healthy), CDR 1 (mildly demented), CDR 2 (moderately demented), and CDR 3 (severely demented). CDR 0.5 (questionable dementia) was included for subjects who were "neither clearly demented nor healthy" (Hughes et al., 1982, p. 569).

Hughes et al. and Rubin, Morris, Grant and Vendegna (1989) followed up subjects with the CDR over time periods ranging from 6 to 84 months. Hughes et al. report the CDR classification for 14 of 16 subjects originally rated CDR 0.5 (questionable dementia) at reassessment six to nine months later. Nine subjects remained unchanged at CDR 0.5; four were rated CDR 1 (mild dementia); and one was re-classified as CDR 0, healthy. Two subjects could not be followed. Rubin et al. describe the results of clinical assessment of 41 subjects, 23 men and 8 women, who received a CDR of 0.5, questionable dementia which in their paper is labelled 'very mild dementia of the Alzheimer type'. They found that the performance of all subjects with CDR 0.5 differed from that of control (CDR 0) and mildly demented (CDR 1) subjects on the DS, cognitive DS, SPMSQ, Sum of Boxes (a rating of 1 to 3 on each of M, O, JPS, CA, HH, and PC), and on the Information-Memory-Concentration Test. The CDR 0.5 subjects differed from CDR 1 subjects but not from CDR 0 subjects on the

aphasia battery. They also looked at the group of 16 CDR subjects identified by Hughes et al., 1982 who were enroled in the research program between 1979 and 1981. Over a period of 84 months, 10 of the 16 had progressed to definite dementia, CDR 1 or greater, one had died and neuropathologic examination had confirmed the diagnosis of AD. Of the remaining 5 subjects, none had progressed by 15 months; by 60 months, two remained at CDR 0.5, one had improved to CDR 0, one was not re-examined (but that one was interviewed by telephone at 84 months and a CDR of 0.5 was assigned), and one had died.

Rubin et al. (1989) report that "the two major conclusions of this study are (1) the CDR 0.5 stage of dementia, defined as 'questionable' cognitive impairment, actually represents very mild SDAT in the large majority of cases, and (2) as a group subjects with CDR 0.5 differ from both controls and subjects with mild SDAT in their performance on several standard clinical cognitive scales" (p. 381). They acknowledge that they were unable to determine whether the CDR 0.5 subjects suffered a very slowly progressive dementia or a non-progressive process, and that performance on the standard clinical batteries they used did not allow differentiation of those who progressed from those who did not. They recognize the homogeneity of the sample as a limitation of their work; patients with any complicating medical, neurologic, or psychiatric disorder were excluded.

In a companion paper to that described above, Storandt and Hill (1989) examined the psychometric test performance of the same 41 subjects. They identified two purposes to their study: (1) to extend their previous work to include *very* mildly demented individuals, and (2) to determine whether those psychological functions affected in the very mild stage are the same ones affected at the mild stage. Earlier work (Storandt, Botwinick, Danziger, Berg, and Hughes, 1984) had suggested that three types of psychological function were impaired in mild SDAT: memory, speeded psychomotor performance, and language. In the current paper, Storandt and Hill sought to determine if the same functions were affected in very mild SDAT.

Storandt and Hill compared CDR 0, CDR 0.5, and CDR 1 subjects on a psychometric test battery. The tests included standard administration of the Wechsler Memory Scale (WMS) Mental Control, Logical Memory, and Digit Span subtests; a self-paced visual recognition test of pairs of words from the WMS

Associate Learning subtest; production of S and P words, the 60 item Boston Naming Test, Benton Visual Retention Test, Bender Gestalt Test, Trail Making Test, Part A, Crossing-Off (a visual cancellation test); and the Information, Comprehension, Digit Symbol, and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS). Canonical correlation was used to determine those measures, and their weights, showing maximum correlation with group membership. The tests showing the greatest correlations were, in order of magnitude, Logical Memory (.70), WAIS Digit Symbol (.35), and Boston Naming Test (.30). Storandt and Hill report "The raw canonical regression equation for the canonical variate was 3.940 -0.332 Logical Memory -0.031 Digit Symbol -0.026 Boston Naming" (p. 385). The means for the canonical variate were control group -1.78, questionably demented 0.31, and mildly demented 2.05. With a cutoff point on the canonical variable of 0, no one in the control group and only three of the mildly demented individuals were misclassified. There was, however, no cutoff point that allowed good discrimination of the questionably demented group as their range of scores on the canonical variate was entirely subsumed by the range found for the mildly demented group, and 40% of the questionably demented group obtained canonical variate scores that overlapped with the scores of the control group.

In discussing their results, Storandt and Hill offer these observations:

> The fact that only one canonical variate was obtained indicates that the three groups vary along only one dimension, presumably the degree of dementia. This result is consistent with an interpretation that those in the questionable group do, indeed, have very mild SDAT. The unimodal shape of the distribution of this group on the canonical variate supports this position, as does an examination of the SDs of the scores on the various tests for this group (Storandt & Hill, 1989, p. 385).

They conclude with the following statement:

> A major difference between the type of information available to physicians in making their clinical judgments and that obtained from the objective psychometric battery relates to previous level of function judged by the physicians on the basis of collateral and subject report. This suggests that it will be necessary to take into consideration premorbid performance if objective measures such as psychological tests

> are to be used effectively in screening for very mild dementia. Good collateral informants often are not available to provide this information. Indicators of earlier levels of performance often used in research on ageing (eg. "hold" tests from the WAIS, such as the Information subtest) are not helpful because they too are affected by this disease. What is needed are baseline levels of psychometric performance in the three identified domains obtained while people are still in their midyears (eg. 40s or 50s). A national effort similar to that of baseline mammograms to be used in the detection of breast cancer in older women is required (pp. 385-386).

Rubin and Kinscherf (1989) investigated psychiatric abnormalities, including personality and affective changes and psychotic symptoms associated with very mild SDAT. They compared psychiatric changes in the same 41 CDR 0.5 (questionable dementia/ very mild SDAT) subjects reviewed in the two previous papers with the same group of CDR 1 (mild dementia) subjects, and controls (CDR 0). The personality changes were determined from open-ended questions concerning mental and physical health, and from responses to 11 items of the DS. The changes observed were classified into "three common, clinically useful groups" (p. 1018) identified by factor analysis techniques in an earlier study. The personality assessment included passive changes (secure-inactive, less cheerful, less responsive), agitated changes (irritable, hyperactive), and self-centred changes. Affective symptoms were based on the Feighner criteria (Feighner et al. cited in Rubin & Kinscherf, 1989). Psychotic symptoms were obtained from open, symptom-specific questions, and were classified into three groups; delusions (usually involving stealing or suspiciousness), misidentification syndromes (beliefs that people were in the house who were not, belief that people on television were alive and in the same room, the inability to recognize one's own reflection in a mirror), and hallucinations.

Rubin and Kinscher (1989) found that the questionable dementia group resembled the control group more closely than the mild dementia group. Only one subject in the questionable dementia group had a psychotic symptom. Patterns of psychiatric changes were, however, noted. Both passive changes and agitation were present in very mild DAT and continued to increase through out the course of DAT. Self-centredness was also present in very mild DAT and

continued to increase until the moderate stage of impairment. Early personality changes were not found to be correlated with more rapid cognitive decline.

Only a few depressive symptoms were significantly different between the questionable dementia group and the control group, and those differences arose primarily in reports of the collateral source rather than in the reports of the subjects themselves. Symptoms showing significant difference between very mild SDAT (CDR 0.5) subjects and controls, *by collateral report*, were low energy, psychomotor change, low interest, and poor concentration. By subject report, the only significant difference between CDR 0.5 and CDR 0 was on poor concentration. None of the subjects developed a major depression "in a several-year" follow-up period, but in initial selection, the study excluded subjects with past or present depression.

Psychotic symptoms, prominent in moderate DAT, were in Rubin and Kinscherf's (1989) study "almost never present until the illness is at least at a mild level; therefore, patients who have substantial psychotic symptoms and very mild cognitive deficits are likely to have illnesses other than, or in addition to, very mild dementia of the Alzheimer type" (p. 1020). They suggest that psychotic symptoms may reflect increased involvement of the temporal lobe in AD and note that, unlike changes in personality and affect, early psychotic symptoms do correlate with more rapid cognitive decline.

Despite the findings that most persons classified as CDR 0.5 progress to a true dementia, as Dawe et al. (1992) comment and the group at Washington University acknowledge, no features were found which discriminate between those individuals who progressed to dementia and those who did not.

This section of the review of literature on differentiating very mild SDAT from the benign memory changes associated with ageing concludes with a study by Mitrushina, Satz, and Van Gorp (1989). Mitrushina et al. examined some putative cognitive precursors in subjects thought to be at-risk for dementia. Two at-risk groups were identified: (1) "outliers", individuals who were identified by test performance which deviated by more than two standard deviations on two or more tests of their battery from the mean of the well group, and (2) patients who had been referred to an Alzheimer and memory disorders clinic with recent complaints of cognitive or memory decline, and

who were reported by themselves or their physicians to have symptoms of progressive decline in cognition or memory for at least six months prior to testing, but who did not yet meet the DSM-III-R criteria for dementia. The at-risk groups were compared with a Well group. All groups were matched on age, education and sex. The groups were also "almost identical" for estimated premorbid Full Scale IQ: Well = 119.2, Outliers = 120.5, and Patients = 118.8.

Mitrushina et al. administered a number of tests which were reduced to 12 variables to facilitate data analysis. The 12 variables were subjected to factor analysis and three factors were obtained: Factor I, a general verbal cognitive/verbal memory factor; Factor II, a nonverbal cognitive/nonverbal memory factor; and Factor III, a speed of processing factor. Analysis of variance on factor scores yielded significant differences among the three groups on Factors I and III, but no group effect on Factor II. T-test comparisons demonstrated significant differences between the Well and Outlier groups on four test variables in Factor I, and one test variable in Factors II and III. No test from among the 12 variables reached significance between the Outlier and Patient groups--the putative at-risk groups.

Mitrushina et al. report that their results indicate that while the Outlier and Patient groups were indistinguishable on the basis of their level of cognitive impairment, each group revealed a different pattern of deviation from the Well group. The Outliers' pattern loaded primarily on Factor I, whereas the Patient group demonstrated deficits on all of the Factor I tests and on a majority of the Factors II and III tests. They interpret their findings as suggesting that the Patient group reveals a more generalized pattern of cognitive deficits while the Outliers exhibit a specific pattern of deficits. They observe, however,

> What remains unclear is whether the two neuropsychological patterns (specific vs. general) reflect qualitative or quantitative differences between the two at-risk groups. Qualitative factors would refer to possible etiological differences (e.g., chronic static vs. progressive lesions, or DAT vs. MID), whereas quantitative factors would refer to possible differences in the severity or stage of cognitive impairment (Mitrushina, Satz & Van Gorp, 1989, p. 331).

This is admittedly a preliminary study, however, it is not clear how the findings of this research as it now stands contribute to the resolution the issues of subtype versus stage or differential diagnosis with which this chapter opened.

CHAPTER SUMMARY

While investigation of AD subtypes yields for some researchers a wide range of presentation of signs and symptoms, and their findings are often complicated by questions of whether they are observing differences in subtype or stage, there is an underlying constant: memory impairment. Memory impairment is as Storandt and Hill (1989), as well as others, comment "a hallmark of the disease" (p. 385). It is perhaps more accurate to say memory *and learning* impairments are hallmarks of the disease.

In reviewing subtypes of AD, Chui et al. (1985) found that language disorder in AD usually follows memory loss and Martin et al. (1986) found greater impairment of learning and memory relative to other cognitive functions regardless of modality examined. In examining differences between DAT and MID, Hagberg and Gustafson (1985) found DAT patients had the greatest declines in verbal and spatial memory; Barr et al. (1992) found that an absence of learning effect over time and supremacy of recency over primacy characterized AD; Budzinski (1986) found that the memory variables of interference and intrusions, semantic memory variables of verbal fluency and confrontation variables, and recognition variables discriminated best between MID/PD groups and SDAT; and Parlato et al. (1988) concluded that verbal memory deficits were more marked in AD than in MID when the groups were matched for general cognitive impairment. Huber and Paulson (1985) found in comparing AD with subcortical dementias, that with AD the initial symptoms involve memory loss which deteriorates steadily throughout the course of the disease. Huber and Paulson found, further, that PD patients produced significantly more story items than AD patients after delay when probe questions were used, that AD patients produced more extra-story items on free recall of stories and more extra-list items on free recall of word lists than did PD patients, and, finally, that AD patients produced more false positives on recognition measures than did PD patients. Finally, research with the CDR found that

performance on the Logical Memory subtest of the WMS showed the strongest correlation with group membership for well, questionable dementia, and mild dementia groups.

These findings support the contention that memory deficits are the hallmark of Alzheimer's disease (Storandt & Hill, 1989). A detailed examination of the memory deficits manifested in AD follows.

CHAPTER 5

REVIEW OF THE LITERATURE--PERSPECTIVES ON MEMORY AND MEMORY DEFICITS IN DEMENTIA OF AN ALZHEIMER'S TYPE

Classification of Memory and Memory Operations

A large number of terms and definitions are used to describe and classify memory and memory functions or operations. 'Sensory', 'iconic', 'echoic', 'primary', 'immediate', short-term', working memory', 'reference', 'secondary', 'recent', 'long-term', 'declarative', 'explicit', 'episodic', 'semantic', 'procedural', 'implicit', 'recognition', 'motor', and 'remote' are all terms used to describe "types" of memory, and no claim is made that this list is exhaustive. Memory functions or operations include 'registration', 'acquisition', 'encoding, 'transfer' 'consolidation' 'retention', 'storage', 'decoding', and 'retrieval'; again, no claim is made that this list is complete. In addition to the above, cognitive psychologists are concerned with a 'central executive system', an 'articulatory loop system', a 'visual scratchpad', 'processing resources', 'activation', 'priming', 'depth of processing', 'elaboration', 'distinctiveness', 'congruity', 'encoding specificity', 'degree of meaningfulness', and other concepts. Further, each class or type of memory, each operation or function, and each concept generates a method of assessment. 'Immediate recall', 'delayed recall', 'short-delay free recall', 'long-delay free recall', 'short-delay cued recall', 'long-delay cued recall', 'recognition', 'forced-choice recognition', 'continuous recognition', 'Buschke selective reminding' 'free selective reminding', cued selective reminding', 'Brown-Peterson test', 'rotary pursuit', backward masking', 'object memory', 'priming' are some approaches to the assessment of memory function. The plethora above is drawn from experimental, cognitive, and clinical approaches to the investigation of memory. This study is primarily clinical; hence some "sorting" of terms relevant to this investigation is required.

Erickson (1990) has provided a useful overview of the classification of memory into its component processes. He has limited his review to include "only those having a broad consensus in the current literature" (p. 159). Table 5.1 is suggested by Erickson's Table 1 (Erickson, 1990, p. 160). Table 5.1 is incomplete. It does not include other potential memory processes:

Table 5.1.

Classification of Memory Processes

Type (Clinical Label)	Includes	Persistence
Sensory		
	Iconic (visual)	250 milliseconds
	Echoic (auditory)	1 to 2 seconds
Primary (Visual and Verbal Immediate Recall, Short-term Memory)		± 30 seconds
	± 7 numbers, words, designs, other "units" of information	
Secondary (Visual and Verbal Recent Memory, Long-term Memory, Delayed Recall)		minutes to weeks or months
	Declarative (explicit)	
	Episodic (events)	
	Semantic (facts)	
	Procedural (implicit)	
	Motor skills	
	Perceptual skills	
	Cognitive skills	
	Priming	
Remote		months to lifetime
	Declarative (explicit)	
	Episodic (events)	
	Semantic (facts)	
	Procedural (implicit)	
	Motor skills	
	Perceptual skills	
	Cognitive skills	
	Priming	

haptic, kinaesthetic, and proprioceptive memory. Kinaesthetic and proprioceptive memory may be subcategories of 'motor skills', but haptic memory is problematic. While haptic memory involves a tactile element which might be classified as a perceptual skill and/or a motor skill, which involve, in Erickson's Table 1 and Table 5.1 here, implicit memory, the identification of a shape or texture would seem to involve explicit declarative memory and perhaps semantic (fact) memory. And there are further complications. Implicit learning is sometimes measured with explicit recall, e.g. Hart,

Kwentus, Wade, and Hamer's (1987) investigation of Digit Symbol performance in mild dementia and depression. Symbols and symbol-digit associations were said to be learned implicitly during the coding task, but that learning was assessed by explicit recall of specific symbols and symbol-digit associations. Additionally, there appears to be a difficulty in separating secondary and remote memory except by operational definition. The problem of classification of memory processes is acknowledged. However, the purpose of this introduction to memory processes is not classification but the identification and specification of terms and processes relevant to this clinical investigation.

Little confusion is likely to arise with regard to sensory memory. The labels used are widely accepted, and sensory memory is seldom investigated in clinical studies of memory loss. Clinical interest in sensory memory change may be limited because "it is unlikely . . . that a modest sensory memory loss would significantly contribute to the observed deficits in secondary memory since primary memory, the next stage of the information processing system, is also relatively unaffected by age" (Poon, 1985, p. 430).

In the clinical literature, the terms 'short-term memory' and 'immediate memory' are more frequently used than is the term 'primary memory' for that aspect of memory that has, for normal individuals, a capacity of seven (plus or minus two) discrete items and a duration, in the absence of distraction, of about 30 seconds. Erickson (1990) states that information entering memory "can be viewed as passing through several storage 'buffers' of differing capacities and duration (p. 159). If sensory memory which has a duration of milliseconds to 1 or 2 seconds is the first, or primary, buffer, then that which is defined as primary memory is the second buffer. Following this logic, secondary memory is "in" the third buffer. And tertiary (remote) memory is in a fourth buffer? Erickson also points out that secondary memory is called 'short-term' in many clinical studies and 'long-term' in most studies by cognitive psychologists. To avoid these difficulties, and to remain consistent with clinical practice, the term 'immediate memory' is selected for this investigation. When there is a potential for confusion in reviewing the work of investigators who have selected other terms appropriate comments will be made.

Labelling 'recent', 'secondary', or, in the terms of cognitive psychology, 'long-term' memory is more problematic. La Rue (1982), for example, uses all three terms in two paragraphs (pp. 94-95) to refer from this aspect of memory with a duration minutes to months and an apparently unmeasurable capacity. Clinically, this facet of memory is measured by delayed recall or recognition. The period of delay, either after initial exposure, or, more frequently, after initial or "immediate" recall, is typically 3 to 45 minutes but on occasion hours, days, weeks or months after the initial learning. While Erickson (1990) may be correct when he suggests that secondary memory "is called 'short-term' in *many* [italics added] clinical studies" (p. 159) the review of literature for this investigation suggests that 'long-term' is used as frequently by clinical psychologists as it is by cognitive psychologists to refer to that aspect of memory that has a duration of minutes to months and that begins to operate when the short-term store exceeds seven items, plus or minus two, for normal individuals. In this investigation, secondary or recent memory will be identified as long-term memory and is defined by the parameters outlined in the preceding sentence.

Labelling remote or tertiary memory is potentially somewhat problematic, primarily because there is no clear "cut-off" point between long-term or secondary memory and tertiary memory. Further, the content of the stores is essentially the same for both secondary and tertiary memory as is shown in Table 5.1. Clinically, remote memory is typically assessed by asking the subject or patient to recall or recognize information that is believed to have been acquired decades earlier. In practice, little confusion arises. The clinical literature appears to favour the term 'remote memory', and it is the label of choice in this investigation.

Erickson (1990) identifies registration, storage and retrieval as the three elementary operations that govern memory function. Registration refers to the initial encoding or acquisition of new information, presumably in the short-term memory buffer. Registration requires "intact attentional resources and conscious effort" (p. 160).

Registration is assessed by having the subject repeat or respond to the information immediately after its presentation. Retention is the storage or consolidation of the information registered and refers to the ability to

retain the information, intact, over time. Consolidation requires the transfer of information from short-term to long-term memory and does not require conscious effort. Retrieval (decoding, recall) refers to the ability to retrieve the stored information and requires conscious effort.

Erickson describes free recall as the "most accurate assessment of the basic retrieval ability" (p. 160) but Grober and Buschke (1987) disagree. They suggest that free recall may reveal only *apparent memory deficit* which is secondary to impairment of other cognitive processes. Grober and Buschke argue that *genuine memory deficit*, memory deficit that persists despite an individuals having exercised effective encoding and retrieval activities, is detected only through controlled cognitive processing and cued recall. In cued recall, cues or hints about the to be retrieved item or items semantic category, physical attributes or other characteristics are provided.

Recognition tasks are, Erickson suggests, a means of bypassing the retrieval process to measure information retained but not readily retrieved through recall. Retention can also be assessed by implicit memory tasks. Implicit memory tasks are more automatic processes and reduce the need for conscious effort than is the case for explicit memory tasks, e.g., free- or cued-recall. Such tasks include priming, word-stem completion, and word-fragment completion. Erickson reports that implicit memory tasks are a more robust measure of storage or retention than are explicit memory tasks and reminds that some amnesic patients exhibit intact implicit memory despite impaired explicit memory.

Erickson (1990) identifies additional "broad memory classifications" that have emerged and that are frequently used in the literature. Those categories are working versus reference memory, episodic versus semantic memory, and declarative versus procedural memory. Reference memory contains recent and remote information gained from previous experience while working memory is memory that is actively being updated by current experiment or experience. Episodic memory refers to information about events occurring at a specific time and place. Semantic memory holds factual information, principles, and associations. Erickson suggests that investigators of amnesia find little basis on physiologic grounds for the distinction between episodic and semantic memory. He holds that a "more anatomically robust distinction is

that of declarative versus procedural memory" (p. 160). Declarative memory essentially subsumes both semantic and episodic memory. Procedural memory is involved in learning and retaining a skill or procedure.

While Erickson's characterization of memory types and operations presents a relatively simple model, and some of his characterizations will be debated by cognitive psychologists, e.g., Craik and Lockhart (1972) who suggest an information processing approach to memory structure, the model is adequate to provide a context within which to begin the examination of memory deficits in dementia of an Alzheimer's type.

Brief Survey of Memory Deficits in AD

When matched to normal controls for age, education, and intelligence scores, individuals with Alzheimer's disease perform more poorly on standardized clinical tests of memory than do the controls, that is, there is a *quantitative* difference in memory performance between AD suffers and normal individuals. This is perhaps the only finding that is not in dispute in discussion of memory deficits in Alzheimer's disease. There is, however, considerable debate as to whether there are *qualitative* differences between the losses sustained in AD and those sustained in normal aging and some amnesic conditions.

Erickson (1990) states that immediate memory is often normal in early AD. La Rue (1982) reports that "Immediate memory has often been reported to be within normal limits for age in the mild to moderate stages of senile-onset dementias" (p. 95). Martin et al. (1985) found that immediate auditory attention or memory span remained relatively unaffected in AD. Others (Vitaliano, Breen, Albert, Russo, & Prinz, 1984; Morris & Kopelman, 1986) find that immediate memory is impaired. The discrepancy arises, in part, on how immediate memory is assessed. If immediate memory is measured by digit or word span, little difference is found, as indicated in Martin et al., if, however, immediate memory is measured by free recall or the Brown-Peterson test, significant differences between AD patients and controls are found. Investigations of impairment in immediate memory are also confounded by the failure to control for or the failure to report degree of impairment in AD subjects. Becker, Boller, Saxton and McGonigle-Gibson (1987) demonstrated

that DAT patients were very significantly impaired ($p < .0001$) relative to normal controls on immediate story recall and immediate recall of a simplified version the Rey Complex Figure.

La Rue (1982) writes that in the mild to moderate stages of dementia, "it is the area of recent memory that pathological disturbances are most readily observed" (p. 95). He reports a study by Miller (cited in La Rue, 1982). Miller compared the free recall performance of 14 subjects with mild presenile dementia and 14 age-matched, normal controls on a list learning test of 12 words. He found that the dementia patients were "slightly less accurate" in remembering last-presented items than were controls, but the dementia subjects were "markedly worse" at remembering the first words on the list. The results were interpreted as indicating that either transfer to, or retrieval from, secondary memory [long-term memory] was an area of substantial deficit in the dementia subjects. Parlato, Carlomagno, Merla, and Bonavita (1988) as well as Barr, Benedict, Tune and Brandt (1992) found, in examining the effect of serial position on learning word lists, that AD patients performed significantly different than controls, and in comparing individuals with MID with AD patients, that AD patients demonstrating a superiority of recency over primacy. Pepin and Eslinger (1989) found, conversely, no such superiority as a function of AD. They did, however, find an effect of severity with severely impaired AD subjects demonstrating superiority of recency over primacy. Martin et al. (1985) found in a study of the effect of serial position with AD patients "the primacy component was not differentially affected" (p. 329). It should be noted, however, that Parlato et. al. used an Italian version of the Rey Auditory-Verbal Learning Test with 15 words while Martin et al. used only eight words--scarcely more than immediate word span. Morris and Kopelman report two studies, in addition to Martin et al. Miller (cited in Morris & Kopelman, 1986), found only a moderate decrease in recency effect for AD patients in one study and "virtual no increase" in a second. Wilson (cited in Morris & Kopelman, 1986) found a moderate decrease in primary memory when measured by free recall but a more substantial decrease in the secondary memory component. In addition to showing very significant impairment of immediate memory in the study already cited, Becker et al. (1987) demonstrated very significant ($p < .0001$) impairment of delayed recall

for stories and the Rey Complex Figure when DAT patients were compared to normal controls. Petersen, Smith, Kokmen, Invik, and Tangalos (1992) report "A recent study from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) *demonstrated* [italics added] that delayed recall is the best discriminatory measure at detecting early Alzheimer's disease" (p. 400).

La Rue (1982) reports that at least in the earlier stages of AD remote memory is well maintained. Morris and Kopelman (1986) offer a contrary view. Morris and Kopelman (1986) cite White et al. and Corkin et al. who found evidence that there was no substantial sparing of remote memory in AD, and conclude "the evidence is in favour of impaired remote memory, which extends to the most distance memories" (Morris & Kopelman, 1986. p. 591).

Unlike other areas of memory, motor learning may be relatively preserved in AD. Eslinger and A. Damasio (1986) compared motor learning in 8 moderately impaired individuals who met the criteria for SDAT and age-matched normal controls on a rotary pursuit task. Although the two groups were significantly different on free recall of a 10-item grocery list and the recognition of unfamiliar faces, the SDAT patients and controls displayed a "similar pattern of motor learning" (Eslinger & Damasio, 1986, p. 3006). The difference in performance between controls and SDAT patients was not statistically significant, but a trend was "possibly evident" at $p = 0.11$. The more interesting finding is, however, that the performance of the SDAT patients as a group improved 161% over the learning trials and every SDAT patient showed improvement. This was a "striking" dissociation from their list learning performance which yielded an essentially flat learning curve and a 73% decline (versus 11% for controls) with delayed recall. On learning unfamiliar faces, the SDAT group began at 85% of the controls, but by the third trial the SDAT group had declined to 66% of controls. At the delayed recognition trial, the SDAT patients had dropped to almost chance level of recognition and showed a 29% decline versus 2% for controls.

This brief survey demonstrates that there is substantial debate regarding memory deficits in AD. The review now turns to a review of memory impairment in AD from the view point of cognitive psychologists. Primary Memory and Working Memory will be reviewed in some detail. The concepts of

episodic and semantic memory will, for reasons to be outlined, receive only the brief review that follows.

Episodic and Semantic Memory

The concepts of episodic and semantic memory were articulated in 1972 in *Organization of Memory* edited by Tulving (cited in Nebes, Martin & Horn, 1984). Nebes, Martin and Horn explain the concepts as follows:

> Episodic memory is an autobiographical record of unique episodes and events in an individual's experience, encoded and maintained in relation to a particular temporal and spatial context. Semantic memory, by contrast, is a relatively context-free thesaurus of organized knowledge regarding words, concepts and their associations, and rules for manipulating these symbols and concepts (p. 321).

One reason for limited treatment of these concepts is a bias in favour of the concepts declarative and procedural memory in agreement with Erickson (1990). It is interesting from this point of view that Knotek, Bayles, and Kaszniak (1990) describe episodic memory as a subsystem of semantic memory as it would be in the declarative-procedural conceptualization. A second reason is that there is little debate that episodic memory, as defined, is impaired in AD. A third reason for brief treatment is the difficulty in separating semantic memory deficits from more general aphasic and attentional deficits in AD, and those difficulties lead to substantial difficulties and debates that may reflect differences in methodology more than differences in substance. Such differences are reflected in Nebes et al. (1984), who find preserved semantic memory, and Knotek et al. (1990), who question some of the methodology used to demonstrate impairment, versus Chertkow and Bub (1990) and Ober, Dronkers, Koss, Delis, and Friedland (1986) who argue that semantic memory functions deteriorate in AD.

INFORMATION PROCESSING APPROACHES TO MEMORY

While the focus of this investigation is primarily clinical, the work of cognitive psychologists has had tremendous impact on memory research on the investigation of immediate, or in their terms, primary or working memory that those concepts must be acknowledged and explored.

Levels of Processing Model

In 1972 Craik and Lockhart published a major paper proposing 'levels of processing' as a framework for memory research in reaction to the multistore model (Broadbent cited in Craik & Lockhart 1972). The multistore model is essentially that outlined by Erickson (1990). Craik and Lockhart noted a number of difficulties with the multistore model.

The first was with the notion of capacity. Craik and Lockhart observed that the exact nature of the limitation of capacity was unclear; was the limitation one of processing capacity, storage capacity or some interaction between processing and storage capacities. They noted that while attempts to measure capacity had favoured the notion of storage limitation, a large range of "capacities" was observed. Measures of memory span for unrelated words, letters or digits was typically between five and nine items, but it was found that young subjects could accurately recall strings of up to 20 words if those words were in a meaningful sentence. Craik and Lockhart concluded that the concept of capacity was better understood in terms of limitation of processing.

Craik and Lockhart also found difficulties with the nature of coding in short-term and long-term memory stores. Earlier formulations (Conrad; Baddeley cited in Craik & Lockhart 1972) had suggested that information in short-term stores (STS) was coded acoustically while coding in long-term stores (LTS) was semantic. Subsequent research showed that information in STS could be acoustic, visual, and perhaps semantic, though the evidence appeared contradictory at times. Craik and Lockhart suggested that the question of coding was more appropriately formulated, like the question of capacity, in terms of processing. They suggested that processing demands were imposed by the experimental paradigm and the nature of the material to be remembered.

The third difficulty with the multistore model that Craik and Lockhart recognized was that model's conceptualization of forgetting characteristics. They argue that if memory stores could be distinguished in terms of each store's forgetting characteristics, then a minimal requirement ought to be that retention in a particular store would be invariant across various experimental paradigms and experimental conditions. Craik and Lockhart acknowledged in their 1972 paper that the invariance of forgetting from STS and LTS had not been rigorously tested, but report that there were cases in

which that invariance clearly broke down, namely in research with retention of paired-associate learning over various experimental demands and with the durability of memory traces for visual stimuli. The position they put forth was that retention was a factor of the experimental paradigm, the nature of the material to be processed, and the subjects ability to use develop systems to analyze and enrich the to-be-processed information. Qualities that interact to influence the processing of information include familiarity, compatibility, and meaningfulness of the material to the subject.

As an alternative to the multistores model, Craik and Lockhart (1972) propose a levels of processing model. They argue that "perception involves the rapid analysis stimuli at a number of levels or stages" (p. 675). Early or preliminary stages of analysis are concerned with physical or sensory features; later stages are concerned with matching the analysis of the sensory input against stored abstractions from past learning. The later stages are concerned with pattern recognition and the apprehension of meaning. This serial or hierarchical processing was referred to as "depth of processing" and "greater depth" implied more extensive semantic or cognitive processing. The term 'depth of processing' was taken by their critics to imply more or less than Craik and Lockhart intended, and in a retrospective commentary (Lockhart & Craik, 1990) on levels of processing as a framework for memory processing Lockhart and Craik note the importance of elaboration and distinctiveness as elements of depth of processing. They argue, however, "Deeper processing is still a sensible notion where deeper refers to the greater involvement of processes associated with interpretation and implication within the relevant domain" (p. 102). Lockhart and Craik remind that depth of processing is not restricted to the linguistic domain, and that greater knowledge and expertise yield deeper processing in any domain. The result of the analysis is a memory trace, and Craik and Lockhart (1972) suggest "that trace persistence is a function of depth of analysis, with deeper levels of analysis associated with more elaborate, longer lasting, and stronger traces" (p. 675). They suggest further that since the organism is normally concerned only with the meaning extracted from the analysis of stimuli, it is usually advantageous to store the products of deep analysis, i.e., the meaning, but there is usually no need to store the products of the preliminary analysis.

In Craik and Lockhart's (1972) levels of processing model, retention is, then, tied to levels of *perceptual* processing. Retention is a function of depth of processing and such other factors as attention to the stimuli, compatibility of the stimuli with existing cognitive structures, and the processing time available. Processing time or speed of analysis does not, however, determine depth of analysis. Highly familiar, cognitively compatible, and therefore meaningful stimuli will be processed to deeper levels and better retained than less meaningful stimuli. Craik and Lockhart comment, further, that while levels of processing may be grouped into stages, e.g., sensory analysis, pattern recognition, stimulus elaboration, and apprehension of meaning, it is more useful to envision memory as a continuum that extends from "the transient products of sensory analysis to the highly durable products of semantic-associative operations"; they continue "However, superimposed on this basic memory system there is a second way in which stimuli can be retained--by recirculating information at one level of processing" (p. 676). They chose the term primary memory (PM) to refer to this operation.

Craik and Lockhart argue that the limited capacity of PM is a function of the processor. The number of items that can be held in primary memory depends upon the level at which the processor is operating. At deeper levels learned rules and previous knowledge are invoked and material can be processed and retained more efficiently. The essential feature of retention in PM is that the material, or aspects of the material is still being processed or attended to; the items are still in consciousness. If attention is diverted information will be lost appropriate to the level at which the item is being processed. Primary memory retention is the equivalent of continuous processing which prolongs an item's high accessibility, but does not lead to the formation of a more permanent memory trace. Craik and Lockhart label this holding in consciousness and recycling as Type I processing, and it is contrasted with Type II processing which involves analysis at deeper levels. They state that only Type II processing should lead to improved retention.

The limited capacity of PM is explained by assuming "a flexible central processor." The "central processor can be deployed to one of several levels in one of several encoding dimensions, and . . . can only deal with a limited

number of items at a given time (Craik & Lockhart, 1972, p. 679). Items are kept in consciousness by continuous rehearsal at a fixed level of processing. The depth at which primary memory operates will depend on the nature of the items to be encoded (familiarity, compatibility, meaningfulness), and the usefulness to the subject of continuing to process at a given level. Craik and Lockhart contend that primary memory, at any level, deals with units or "chunks", that is, a sound, a letter, a word, an idea, or an image, and not a constellation of attributes, is rehearsed. This notion of rehearsal is developed more fully in the research on working memory.

Working Memory Model

The concept of working memory was developed by Baddeley and Hitch (cited in Lockhart & Craik, 1990) and refined by Baddeley (1986). Working memory is dived into three "subcomponents": (1) the central executive, an attention-controlling system; and two "slave systems", (2) the visuospatial sketch pad which manipulates visual images, and (3) the phonological loop which stores and rehearses speech-based information. Working memory, like primary memory in Craik and Lockhart's (1972) model, is "the system that is necessary for the concurrent storage and manipulation of information" (Baddeley, 1992, p. 556). Within Baddeley's model, the phonological loop, has been investigated most extensively.

The phonological loop has two components. One is a phonological store that holds acoustic or speech-based information for one or two seconds. The second component is an articulatory control process which is described as being analogous to inner speech, i.e., subvocalization. The articulatory component serves two functions: (1) to maintain material within the phonological store through repetition or rehearsal, and (2) to register and rehearse visual information that can be verbally "labelled" in the phonological store through subvocalization. Like PM, working memory, depends on continuous attention (Morris & Baddeley, 1988).

The visuospatial sketch pad is less well understood. There appear to be separable visual and spatial components. The visual component is concerned with the representation of the pattern of information, that is, with visual features, while the spatial component is concerned with the relationships of

visual elements. The visuospatial sketch pad is also highly susceptible to distraction through novel or irrelevant visual stimuli.

The central executive is an attentional control and executive or planning system that directs and coordinates the function of the slave systems. The central executive has a limited processing capacity and disruption of rehearsal in the slave systems is thought to reflect the "using up of processing resources" (Morris, 1986, p. 80). The complexity of the central executive system is acknowledged because it "must communicate with a range of mental processes that are likely to have neuroanatomical substrates in different areas of the brain" (Morris & Baddeley, 1988, p. 292).

It is not clear that Primary Memory in a levels of processing model and working memory are irreconcilable except to those who for one reason or the other have chosen a dogmatic position. Lockhart and Craik ask

> Is the concept of working memory as proposed by Baddeley and Hitch (1974) and developed by Baddeley (1986) analogous or identical to this view of primary memory as an active processor? The concepts clearly share some features: Both primary and working memory are processors as opposed to passive memory stores, and both deal with various types of information. But whereas the Craik and Lockhart concept of primary memory is a set of processing activities carried out in various parts of the cognitive system, Baddeley's working memory appears to be more structural, located in one place and receiving, integrating, and managing different types of information. The core of Baddeley's working memory is the *Central Executive* whose function is to co-ordinate the activities of such peripheral slave systems as the articulatory loop and the visuospatial sketchpad. But what is the nature of the Central Executive? Can its capacity or its managerial prowess be independently measured? In the absence of satisfactory answers to such questions, it is difficult to see how the concept escapes Baddeley's (1978) own criticisms of levels of processing that the ideas are poorly defined, too general, and not easily amenable to measurement (Lockhart & Craik, 1990, p. 105).

It should be noted that the Craik and Lockhart's model is not without something very like a Central Executive. In their 1972 paper they "endorse

Moray's (1967) notion of a limited-capacity central processor which may be deployed in a number of different ways" (Craik & Lockhart, 1972, p. 676), and one must assume that there is some executive system that shunts incoming stimuli to the domain and to the level at which it can be optimally processed.

It is doubtful that the "real" debate between Craik and Lockhart is about memory processes. It is, rather, a debate in the philosophy of science. The nature of the question at issue is presented in Lockhart and Craik (1990). The crux of the debate is "whether it is more profitable to induce broad general principles and then use experimentation as a sort of dialogue with nature to refine the concepts in question, or more profitable to postulate smaller-scale mechanisms and structures whose reality can be confirmed through various types of experimentation" (Lockhart & Craik, 1990. p. 93). They suggest that Baddeley holds the latter position in his 1978 critical assessment of levels of processing. They assert in reply "This is not an either/or matter, since obviously we need both principles and mechanisms. Mechanisms must be located within a larger cognitive architecture that embodies general principles: a general theory of memory cannot be constructed by merely assembling mechanisms" (Lockhart & Craik, 1990. p. 93).

Measuring Memory

Alzheimer's disease research growing out of models of levels of processing and working memory has tended to use similar methods of investigation or experimental paradigms. Both have favoured free recall with a focus on primacy and recency effects, memory span, and forgetting as assessed through Brown-Peterson type tasks as well as a modification of that paradigm sometimes referred to as a dual-task condition.

While free recall may be measured in a number of ways, recall of a verbal narrative, visual designs, list learning, and others, list learning has been used most frequently because it offers the researcher greater experimental control and offers the opportunity to assess new learning in the number of words recalled as well as primacy and recent effects with various subject groups. Martin et al. (1985) required subjects to learn four word lists while encoding conditions were manipulated. One condition was "free" encoding, i.e., words were simply read and shown to the subjects; a second condition required the subject to provide a rhyming word as the target word

was presented; a third condition asked the subject to state where the word could be found; and a fourth condition required the subject to pantomime a movement or series of movements associated with the word's use. In another experiment reported in the same paper, Martin and his colleagues examined the effect of serial position (primacy versus recency) on recall with an 8 word list. In reviewing a number of papers, Morris and Baddeley (1988) report that if AD subjects are required to learn a word list, they are more likely to recall the last items of the list. They also report that phonological similarity interfered with list learning.

From a levels of processing perspective, variation on list recall under different encoding conditions is interpreted as a depth-of-processing effect and the failure of AD patients to encode stimulus attributes sufficiently. Martin et al, (1985) failed to find a significant primacy component with free recall, though they acknowledge that had their 8 word list been longer that effect may have appeared. They did find that with a recognition paradigm in which the target word, a phonemic, semantic, and unrelated distractor, AD subjects incorrectly selected the semantic distractor significantly more often than either the phonemic or unrelated distractor. Martin et al. interpreted this result as inadequate semantic analysis of the to-be-remembered verbal information. Morris and Baddeley (1988) report on the basis of their review that there is "at most, only a slight reduction in performance on the recency portion of free recall" (p. 283). They acknowledge Wilson et al. (cited in Morris & Baddeley, 1988) who suggested the deficit was partially a result of an encoding deficit, and Martin et al. cited above, but argue that impairment of the "control processes of working memory is a sufficient cause of the primary memory deficit in AD" (p. 283). It is not clear how this advances interpretation of the phenomena as the "control processes", i.e., the Central Executive, encompasses both attention and processing.

Memory span is measured by the subjects recall of a list of items, digits, letters, words, or Corsi blocks in correct serial order. Morris and Baddeley (1988) report that most studies have found that AD patients are mildly to moderately impaired on these tasks. Memory span can be manipulated by presenting items that are phonologically similar or dissimilar or in the case of words by increasing word length. Phonological similarity and increasing word length decreases memory span with both AD patients and normal

subjects. The working memory model explains these effects in terms of the Articulatory Loop System. The phonological effect is "thought to occur because phonologically similar material will have similar, and thus more easily confused, codes within the store" Morris & Baddeley, 1988, p. 288). The notion of distinctiveness in the levels of processing model would appear to account for the effect equally as well. In the working memory model, word-length effect is explained in terms of slower and, therefore, less efficient rehearsal. Word-length effect is also amenable to explanation in terms of "processing time available" in the levels of processing model.

Forgetting is most frequently measured through the Brown-Peterson task which requires the subject to retrieve three verbal items (frequently consonant trigrams, but also words) after a period of distraction (counting backward by 2s or 3s from a three digit number, articulating an irrelevant word, recalling digits, reversing digits) over various periods of delay (usually a matter of seconds, 2, 5, 10, 20). A frequent variation is to require the subject to engage in some non-verbal task, e.g., tapping, during the delay interval. Morris (1986) reports that when there was no distractor task, SDAT patients and normal controls showed minimal forgetting, though he acknowledges that a ceiling effect may have obscured potential differences between the groups. However, with any intervening task, articulation of the word 'the', digit reversal, digit addition, or tapping, SDAT patients performed significantly more poorly than controls. SDAT patients also performed significantly worse with increasing periods of delay, but here performance at "approximately floor levels" by this group limits the significance of this experiment.

The investigation by Morris described above was within the context of working memory and is interpreted as reflecting the impairment of the central executive system. There is, however, nothing that prohibits an equally creditable analysis in the language of the levels of processing model.

In a study of short- and long-term forgetting for both verbal and non-verbal material in Alzheimer's disease, Becker, Boller, Saxton and McGonigle-Gibson (1987) found, without equating initial encoding and using only slightly modified versions of frequently used clinical instruments, i.e., the Rey Complex Figure and Story Recall, that patients with AD have normal rates of forgetting and that their rate of forgetting was not related to the overall

severity of their disease. The study is from a levels of processing perspective, and Becker et al. (1987) concluded that the "AD patients' memory deficits may be due . . . to an inability to encode a sufficient number of stimulus elements or features, hampering later recall" (p. 69).

Quantitative Versus Qualitative Differences

Findings from research from the working memory and levels of processing models have been interpreted to show that memory in AD patients is *quantitatively but not a qualitatively* different than that of controls. Morris (1986), using a working memory model, states with regard to forgetting using Brown-Peterson tasks with digit reversal and digit addition as distractor tasks for control and SDAT groups, "If the zero delay condition is excluded, the forgetting curves for the two groups in the digit reversal and digit addition conditions *are parallel* [italics added] (p. 87). Martin (1985), using a levels of processing model, found that "while the ability of AD patients to learn word lists was appreciably diminished, their pattern of performance as assessed by analysis of learning rate, serial position effects, and the relation between primary and secondary memory did not differ from the patterns established by normal individuals" (P. 331). Kopelman (1985) reporting an experiment examining rate of loss from primary memory with a Brown-Peterson test, new learning with the Wechsler Logical Memory test, and forgetting from secondary memory with a picture recognition task, observed "once information had been acquired in secondary memory, the Alzheimer patients . . . displayed a normal forgetting rate" and "the Alzheimer group did *not* display accelerated forgetting from secondary memory" (p. 537). Corkin (cited in Morris and Kopelman, 1986) found "the performance of mildly impaired AD patients matched controls at 10 min and at 72 hr with a curious disparity of performance at 24 h" (p. 587). Becker et al. (1987), using more typical clinical measures and investigating from a levels of processing perspective, draw similar conclusions regarding memory deficits in AD: "recent evidence suggests that while there are quantitative differences among the performances of patients with amnesias of differing etiologies, there do not appear to be qualitative differences" (p. 70).

Whether approached from a working memory model or a levels of processing model the conclusion of the cognitive psychologists' AD research is the same, which is, in paraphrase, that AD patients do not have forgetting problems, they have acquisition problems.

The clinical psychologist is, on the other hand, rarely confronted with individuals complaining that they have acquisition problems. The concerns of the individuals a clinical psychologist meets are about the *quantitative* changes in their memory. And the clinical psychologist's concern is not does this patient have an acquisition deficit or a forgetting deficit, but do this individual's perceived quantitative memory deficits arise from AD, MID, Binswanger's disease, depression, PD, or some other disorder. Morris & Kopelman (1986) comment on the roles of clinical and cognitive psychologists in AD. Noting that most aspects of memory, primary (or working), secondary, remote, and semantic, are implicated in AD, they see the roles for clinical and cognitive psychologists as follows:

> Clinical psychologists have an important role to play in developing tests that will identify these problems, for use in early diagnosis . . . and the assessment of the efficacy of treatments. However, the challenge for cognitive psychologists is to construct some theoretical account of the nature of the impairments in light of current models of memory. Drawing together the research into a coherent framework is particularly challenging in the light of the diversity of theoretical models of memory (p. 576).

The concern of this investigation is clinical and is to determine if a widely used memory test, the Wechsler Memory Scale--Revised, is an adequate instrument for the early and differential diagnosis of Alzheimer's disease. As such it conforms to the role Morris and Kopelman see for clinical psychologists.

Chapter Summary

This chapter has outlined a range of terms and concepts used to discuss memory from the perspectives of both clinical and cognitive psychology. The review by Erickson (1990) reflects, primarily, a multistores perspective that is debated by some cognitive psychologists. Some aspects of approaches by

cognitive psychologists, levels of processing as articulated by Craik and Lockhart (1972) and Lockhart and Craik (1990) and working memory as conceptualized by Baddeley and Hitch (1974) and Baddeley (1986), were reviewed. That review focused mainly on aspects of immediate memory, or in the terms of those authors, primary memory (Craik & Lockhart, 1972) and working memory (Baddeley & Hitch cited in Lockhart & Craik, 1990; Baddeley, 1986), as it is in that area of memory research that the models are best compared and contrasted. The preferred experimental paradigms of the cognitive psychologists using those models were examined briefly.

The research in cognitive psychology from the levels of processing and working memory has tended to attribute memory problems to problems of acquisition and has argued that while there may be quantitative differences in memory between normal individuals and DAT patients, there are no significant qualitative differences.

Other research was reviewed that identified areas of quantitative differences between AD patients and normal controls and/or other demented or amnesic groups. That research indicates that relative to normal individuals of comparative age, AD suffers are, when other factors, education, IQ scores, sex, and other demographic variables, are held constant, quantitatively impaired on immediate memory, long-term memory, and remote memory.

Immediate memory may be measured both by memory span and immediate recall or recognition, and somewhat different results for DAT patients are obtained depending on which aspect of immediate memory is examined and the measurement technique used. Immediate memory is often within normal limits (Erickson, 1990; La Rue, 1982; Martin, 1985) when measured by memory span. When, however, immediate memory is measured by free recall of a word list or the Brown-Peterson test, DAT patients are impaired relative to normal individuals (Vitaliano et al, 1984; Morris & Kopelman, 1986). It should be noted, however, that DAT patients perform in the same range as normals on the Brown-Peterson test if there is not a distractor task. Becker et al. (1987) demonstrated that DAT patients were impaired on immediate story recall and immediate recall of the Rey Complex Figure.

Word lists span the immediate and long-memory distinction. When the number of words in the list exceeds memory span, some words must be held in long-term or secondary memory creating a serial position effect. The words

presented first must, if the list exceeds memory span, be held in long-term memory while the last words are held in immediate memory. When a longer word list is used, most studies find primacy and recency effects; DAT patients remember the last words of the list (recency) better than the first words of the list (primacy) (Miller cited in Morris & Kopelman, 1986; Parlato et al., 1988; Barr et al., 1992). Becker et al. (1987) found significant impairment of secondary memory on in DAT subjects relative to controls is story and visuospatial recall, and Peterson et al. (1992) reported that delayed recall is the best discriminatory measure in detecting early Alzheimer's disease.

Remote memory may be relatively preserved in early DAT (La Rue, 1982), but others report that here is no substantial sparing of remote memory in DAT (Morris & Kopelman, 1986). In a Swedish study, Bäckman and Herlitz (1990) demonstrated that recognition of dated faces (public figures from the 1940s) was significantly poorer in patients with mild DAT than in normals.

The literature reviewed in this chapter and the previous chapter demonstrates that there are significant differences between individuals with DAT and the normal elderly, and between DAT patients and individuals suffering other forms of dementia. The premise advanced in the next chapters is that it is reasonable to hypothesize that individuals inflicted with DAT will present a profile of scores on a memory battery composed of subtests that measure several facets of memory that is different from the profiles of both the normal elderly and individuals suffering other dementias when quantitative differences, that is, the pattern of higher and lower scores, are examined.

CHAPTER 6

REVIEW OF THE LITERATURE--THE WECHSLER MEMORY SCALE--REVISED

The efficacy of the Wechsler Memory Scale--Revised in discriminating Alzheimer's disease or dementia of an Alzheimer type from other forms of dementia is the subject of the investigation proposed. While the original Wechsler Memory Scale continues to be widely used, an increasing number of papers are appearing that have used the revision of the original instrument to investigate memory, and as will be seen in the review that follows, the Wechsler Memory Scale--Revised has generated a substantial amount of research in its own right. The strengths and weaknesses of the Wechsler Memory Scale--Revised are best understood by beginning with an examination of the instrument it is designed to replace.

The Wechsler Mmemory Scale (WMS)

David Wechsler introduced the WMS in a 1945 issue of the *Journal of Psychology* in an article entitled "A standardized memory scale for clinical use" (cited in Prigatano, 1978). According to Prigatano (1978) Wechsler developed the scale over 10 years of "intermittent experimentation". The WMS was conceptualized as an instrument that would reflect memory function relative to other cognitive abilities, but it is generally agreed that the WMS primarily reflects short-term verbal memory function relative to other cognitive functions.

The WMS is comprised of seven subtests: (1) Personal and Current Information, (2) Orientation, (3) Mental Control, (4) Logical Memory, (5) Memory Span, (6) Visual Memory, and (7) Associate Learning. The raw scores for each of these subtests are summed and an age-correction factor is added to the sum to obtain a Memory Quotient (MQ). The MQ is the only "interpreted" value; no subtest scaled scores, similar to those used with the Wechsler intelligence tests, were constructed.

The Personal and Current Information and Orientation subtests consists of questions such as age, date of birth, the name of current public officials, time, and date. The Mental Control subtest requires the examinee to count backward from 20, recite the alphabet, and count by threes "beginning with

one" within time constraints. Logical Memory requires recall as many of units of information as possible immediately following the oral presentation of each of two short stories. Memory Span is the familiar Digit Span test with recall of digits forward and backward. Visual Reproduction requires the examinee to reproduce from memory, after a brief initial exposure, three geometric designs. Associate Learning is a verbal paired associates test in which the examinee is requested to provide the second word of a pair of words previously presented when the examiner provides the first word of the pair.

Prigatano (1978) identifies four psychometric problems with the WMS: (1) a small and restricted standardization sample resulting in inadequate norms; (2) limited information about the reliability of the test; (3) disagreements over the factor structure of the instrument which raises questions regarding its validity, and (4) "the meaning of the Memory Quotient and whether it measures something other than IQ" (p. 4).

According to Prigatano, Wechsler initially described the norms provided with the test as "provisional norms", but those "provisional norms" remained essentially the only norms for an adult population. The standardization sample was drawn from 200 normal subjects ranging in age from 25 years to 50 years at the Bellevue Hospital in New York. The only description of the subject population was that they were "not hospital patients" (D'Elia & Satz, 1989). Those norms were extrapolated to younger and older populations. D'Elia and Satz (1989) suggest that Wechsler's normative data were actually derived from a 96-subject subset--subjects for whom he had Wechsler-Bellevue IQ scores--of the 200 subjects in the reported normative sample. There are other difficulties with the norms. While Wechsler reported that both men and women were included in the sample, the percentages of each sex were not reported; neither were any sex differences in subtest performance reported. Since its appearance a number of normative studies of the WMS with other populations have been generated. Many of those studies are described in both Prigatano (1978) and D'Elia and Satz (1989).

Prigatano (1978) describes the reliability studies of the WMS as "varied" and "unsystematic", but he indicates that they do suggest the following. Test-retest reliability with the same form is "fairly stable" for both subtests and for total score, though no numerical estimates were available when he wrote his summary. The best estimate of alternate-form

reliability, based on published research at the time, was in the "low .80s". The total scores tended to decline with age, but the MQ with the age correction added remains "fairly stable". And, the MQs of psychotic patients, especially those hospitalized for a long time, tended, as would be expected on the basis of clinical experience, to be quite variable.

Factor analytic studies of the WMS have yielded somewhat different factors depending on the group studied. Davis and Swenson (1970, cited in Prigatano, 1978) reported two major factors when they analyzed the WMS subtest scores of a large (N = 622) combined group of neurological and psychiatric patients. Information, Orientation, Logical Memory, Visual Reproduction, and Associate Learning clustered on a Memory factor while Mental Control, Digits Forward, and Digits Backward clustered in a Freedom-from-Distractibility factor. Dujovne and Levy (1971, cited in Prigatano, 1978) conducted factor analytic studies with both a combined neurological and psychiatric group and a normal group. While they used a different factor analytic method and a different sorting of items, they found similar factors. A Freedom-from-Distractibility factor (Mental Control and Digits Forward and Backward) was found that accounted for 31% of the variance and a Memory factor (Logical Memory, Visual Reproduction and hard Associate Learning items) that accounted for 37% of the variance. Dujovne and Levy did not include the Information and Orientation subtests, but they did find a clustering of correlations on the associate learning items among the patient group which they described as Associative Flexibility. Prigatano reports that they described Associative Flexibility as "a learning factor that was very sensitive to gross brain disturbances" (p. 8). Kear-Colwell (1973, cited in Prigatano, 1978) conducted a factor analytic study with another patient group who had been referred for psychological assessment in a general hospital and found essentially the same memory and attention or Freedom-from-Distractibility factors. The Kear-Colwell study did included the Information and Orientation subtests and those items formed a third factor.

Prigatano reports that studies with normal groups have found Memory or "General Retentiveness", "simple learning", and "associated flexibility" factors" (p. 8), but that the Freedom-from-Distractibility factor does not emerge as distinctly as in the patient groups.

The Wechsler Memory Scale--Revised manual (Wechsler, 1987) reports additional WMS factor analytic studies and suggests that the same three factors emerge: I. Logical Memory, Visual Reproduction, Associate Learning; II. Mental Control, Digit Span; and III. Personal and Current Information, Orientation (p. 65). The manual does concede, however, that "Still unclear from this review are the questions of whether or not tests of immediate and delayed recall of learned material have the same factorial composition, and whether or not forward and backward repetition of digits are equivalent measures" (p. 68).

The first validity question Prigatano sets is "MQ and IQ: Do they measure the same thing" (p. 9). He notes that for normal adults with average IQs, the MQ and IQ are probably measuring much the same thing. For adults with IQs in the Superior range the correlation between IQ and MQ is reduced. For adults with average ability the correlation between MQ and IQ is .85, but for adults in the Superior range the correlation drops to .40. A study in a rehabilitation centre that included brain damaged patients, mentally retarded, and normals whose IQs did not exceed the average range found a correlation of .80 between IQ and MQ. Despite these correlations, Prigatano suggests that IQ and MQ do not appear to be measuring identical functions in all individuals. He reports studies with patient suffering Wernicke-Korsakoff Syndrome whose IQ scores were within the normal range, but whose MQs were 16 -20 points lower, and his own 1974 work (Prigatano, 1974 cited in Prigatano, 1978) comparing patients with head injuries resulting in unconsciousness with psychiatric patients found an IQ-MQ discrepancy of 10.07 (significant at .01) for HI patients, but a difference of only -2.42 for the psychiatric group.

In his review of studies, Prigatano (1978) concludes that the WMS is a valid test of short-term verbal memory. The WMS-R manual, in its review of the WMS studies of the validity of the WMS MQ concludes that

> the Memory Quotient of the *Wechsler Memory Scale* is sensitive to many, but not all kinds of memory problems; that it seems most affected by defects of verbal memory and to disturbances or lesions of the left cerebral hemisphere; and that other, more detailed kinds of assessment may be needed for differential diagnosis of particular memory disorders (Wechsler, 1987, p. 69).

Prigatano summarizes the strengths and weaknesses of the WMS in his 1978 review. The strengths of the test include the finding that total scores decline with age as predicted theoretically; there is a relatively constant factor structure; MQ scores usually fall below Full Scale IQ scores in patients with established amnestic disorders; and experimental support for the construct validity of the WMS as a measure of short-term verbal memory. The weaknesses he finds include the absence of scaled or standard scores for the subtests; problems with scoring Logical Memory; the absence of norms for a large representative sample; and the need for restandardization of the MQ with the WAIS and/or WAIS-R rather than the Wechsler-Bellevue. Prigatano concludes that the "WMS needs to be improved substantially if it is to continue as a viable measure of memory function" (Prigatano, 1978, p. 15).

Revised Wechsler Memory Scale (RWMS)

A short-lived but apparently influential, given the changes that emerge in the WMS-R, attempt to revise the WMS came with Russell's Revised Wechsler Memory Scale (RWMS) (1975 cited in O'Grady, 1988). The RWMS used only the Logical Memory and Visual Reproduction subtests of the WMS but introduced a period of delay and a percent retention measure. With Russell's revision, Logical Memory and Visual Reproduction were administered twice with a 30 minute delay between administrations, and scores for immediate and delayed recall were recorded. The percent retention score was calculated from the delayed recall score/immediate recall. Six scores were obtained: verbal memory immediate and delay; visual memory immediate and delay; and percent retention verbal and visual.

O'Grady (1988) reported that while the RWMS appeared to be widely used in clinical settings, there is only limited published research on its "capabilities and limitations". Such studies as existed indicated that the RWMS could discriminate dementia from normal aging, and in Russell's own research with a group of brain damaged patients and a group with no neurological symptoms, the normals scored significantly better on all scores of the RWMS (Wechsler, 1987). O'Grady's research indicated that the RWMS performance was unrelated to psychopathology or race, and that the RWMS was "substantially" less associated with IQ than was the original WMS. He found, on the other hand, the discriminant validity of the RWMS uneven within itself

and with other measures of ability. The immediate and delayed measures showed "good discriminant ability", but neither of the retention measures did. O'Grady reports that "retention scores based on percentages of original learning do *not* control for the amount of learning" and suggests that "it may be worthwhile to consider the adoption of some other method of measuring retention, or the development of some actuarial or normative approach to a retention score" (O'Grady, 1988, p. 326).

The Wechsler Memory Scale--Revised (WMS-R)

The manual for the WMS-R, in describing the rationale for a revised instrument, acknowledges the limitations described by Prigatano but makes no mention of Russell, yet his work with delayed recall was obviously considered. The rationale reports the following limitations of the original scale:

> the original scale includes only one subtest that measures memory for visual material and therefore the WMS total score reflects mostly verbal memory. The memory-related subtests of the WMS focus entirely on short-term recall, and thus lack measures of long-term retention of learned material, a function that research and clinical experience has shown to be significant. Furthermore, the single summary score of the WMS, the Memory Quotient, permits no differentiation of separate memory functions (Wechsler, 1987, p. 1).

To address these, and other, limitations, the revision included the following changes: (1) norms stratified at nine age levels; (2) replacement of the MQ with five composite scores; (3) the addition of new subtests measuring figural and spatial memory; (4) the addition of delayed recall measures; and (5) the revision of scoring procedures for several subtests to improve scoring accuracy (Wechsler, 1987, p. 2).

Loring (1989) comments on the revisions and finds that the WMS-R has "addressed many of its predecessors' short comings." He continues that due to its "relatively strong psychometric grounding and representative normative sampling, the WMS-R will likely obtain a prominent position in many neuropsychological batteries." Loring does, however, have some reservations, and he "presents some preliminary concerns regarding the test's construction

that he believes require consideration "prior to its widespread implementation" (p. 59).

Norms

The WMS-R manual reports that "the standardization sample for the WMS-R was designed to represent the normal population of the United States between the ages of 16 years 0 months and 74 years 11 months" (p. 43). Demographic data were drawn from the 1980 U.S. Census reports and other more recent special-purpose census reports. Demographic features considered include age, sex, race, geographic region, education, and IQ. The standardization sample included 50 cases at each of six age groups: 16-17, 20-24, 35-44, 55-64, 65-69, and 70-74. Norms for age groups 18-19, 25-34, and 45-54 were interpolated from the performance of other groups. Citing Guilford (1965) and Hayes (1963), the manual states that 50 cases are considered sufficient to provide stable estimates of the population mean.

Loring (1989) acknowledges the WMS-R manual's assertion that 50 subjects are considered an adequate sample for deriving a population estimate, but points out the contrast in sample size between the WMS-R standardization and other instruments standardized at about the same time. The Wide Range Achievement Test--Revised and the Peabody Picture Vocabulary Test-Revised were normed on 200 subjects per decade while the Stanford-Binet Intelligence Scale, and the Wechsler Intelligence Scale--Revised included 200-300 subjects per age group. The effect of using 50 subjects rather than 200 yields, according to Loring, estimated population means that are half as stable, that is, the standard error of the mean doubles. Loring also has reservations about the interpolation of means for the three age groups identified above based on the assumption of a linear decline. He argues "the assumption of a linear decline is untenable unless one argues that this is an artifact of relatively unstable estimates of the mean" (Loring, 1989, p. 61).

Composite Memory Scores

As previously noted in the review of literature, Loring points out that composite scores obscure patterns that may be clinically relevant. Loring expresses concern that the General Memory Index (GMI), which is analogous to the MQ, may be treated as the MQ-R in many contexts, and he demonstrates that

the GMI, like the MQ, is weighted in favour of verbal memory. He observes that of the 193 weighted points contributing to the GMI, 124 are derived from the verbal subtests while only 69 are derived from the visual subtests. He offers the following example of the outcome of that difference.

> Consider two patients with Verbal and Visual Memory Indexes of 100 and 74 using Table C-1 from the WMS-R manual, p. 128 for 55- to 64-year-old subjects. When the higher index is verbal and the lower index is visual, a composite index of 91 (27th centile) is obtained. In contrast, when the opposite pattern is observed (verbal=74, visual=100), a composite index of 84 (14th centile) is derived. This 7-point difference exceeds the standard error of measurement for the General Memory Index . . . (Loring, 1989, p. 62).

There are difficulties with the Visual and Verbal Indexes as well as with the GMI. Loring reports on the basis of studies in the manual (Wechsler, 1987, pp. 84-85) that those indexes were unable to differentiate epilepsy patients whose seizures originated in the left temporal lobe from those whose seizures originated in the right temporal lobe. The indexes also not only failed to correctly identify patients who had undergone either a unilateral left or right anterior temporal lobe resection, but in some cases incorrectly suggested the lobe that had not been resected (Loring, Lee, Martin, & Meador, 1988). Further, Chelune and Bornstein (1988) found, in working with patients unilateral lesions, a right-left difference only for the Verbal Memory Index, and that the difference was so small relative to the variability that statistical significance ($p < .009$) was obtained, Loring argues, only through a relatively large sample size (N=115).

The WMS-R manual devotes a page and a half (pp. 51-52) to the discussion of development of scoring weights for the composite scores. Herman (1988) summarizes that discussion.

> Three methods of weighting the subtest scores were tried out: (1) Summing the unweighted raw scores, (2) Weighting the raw scores on each subtest in proportion to the reciprocal of the subtest's standard deviation, and (3) Weighting the subtest raw scores in proportion to the reciprocal of the subtest's standard error of measurement. The third method was chosen for it appeared to be the best of the three in terms

> of two outcomes, maximizing the reliability of the composite scores, and differentiating between members of the standardization sample and members of a mixed clinical group used for a series of validity studies of the revised scale (Herman, 1988, p. 105).

Loring (1989) comments with regard to the composite scores that "cognitive theory should determine the relative contributions of material-specific forms of memory, rather than developing memory composites based solely on psychometric considerations designed only to maximize composite score reliability" (p.62).

New Subtests

The WMS-R manual provides little information on the rationale for development of the visual subtests other than that during the late 1970s the prototypes for these tests were "prepared and tried out experimentally along with portions of the existing *Wechsler Memory Scale*" (p. 43). The new tests were Figural Memory, a visual recognition task; Visual Paired Associates, a visual conditional associations task; and Visual Memory Span. The last two are visual analogues of the Verbal Paired Associates and Digit Span subtests.

Loring (1989), drawing on a preliminary factor analytic study described in the WMS-R manual (p.76), states that Figural Memory loads substantially, but not exclusively, on the attention/concentration factor, that it is a "measure of higher-order visual attention span", and that it does not measure retention of visual/figural information over time, i.e., there is no delay measure of Figural Memory. He acknowledges Bornstein and Chelune's (1988) data that suggests that Figural Memory loads more heavily on a nonverbal factor than either the verbal or attention factors when immediate and delayed recall trials are entered into the analysis, but argues that because both immediate and delayed recall performance are included in a single factor-analysis, "the test themselves will cluster into separate factors based upon the high immediate/delay performance correlations" (Loring, 1989, p. 63).

Visual Paired Associations, Loring argues, contains a significant verbal component because "almost all patients spontaneously employ verbal labeling during performance" (p. 63). He suggests that reversing the presentation, that is, presenting the colour and having the subject identify the design

would lessen verbal mediation. This is not a compelling argument. Loring suggests that test makers have a tendency to develop right-hemisphere analogues of left-hemisphere tests by substituting spatial for verbal stimuli, but, given that the hemispheres are specialized for different tasks, there is no "*a priori* reason" to assume that changing words to figures will create a right-hemisphere measure. He seems to have fallen into a similar trap in suggesting that reversal of stimuli and target would lessen verbal mediation; there is no *a priori* reason to assume reversing the order of presentation of stimuli will change the task. It is most likely that verbal encoding takes place during initial exposure when the figure and colour are juxtaposed, and it is not inherently more difficult to encode "golf green" than "green for golf" or "the cannon is red" than "red cannon" as verbal mediators.

It might be argued, more directly, that the analogy between the verbal and visual paired associates tests breaks down because there are no "easy" Visual Paired Associates items. Clinical experience suggests that even moderately impaired individuals can learn all or most of the "easy" Verbal Paired Associates while the same individuals often perform at little more than chance level on the Visual Paired Associates. "Easy" visual paired associate items would have to draw on patterns that have some relationship in visual "schemata" analogous to the semantic relationships in the "easy" verbal paired associates.

Loring (1989) does not comment on the Visual Memory Span subtest in his criticism of the new subtests. The Visual Memory Span subtest is, essentially, a two-dimensional version of a well-established test of visual memory span, the Corsi Blocks and as such is not, in its conception, psychometrically problematic. However, unlike the Corsi Blocks, the printed pattern of squares offers no "backsides" on which to place numbers to guide the examiner when touching the squares; hence, reliable administration requires practice and experience.

Delayed Recall

Clinical experience suggests the value of delayed recall measures (Prigatano, 1978; Bornstein & Chelune, 1988; Loring, 1989). Comparison of the GMI and the Delayed Recall Index (DRI) can indicate a relative inability to

retain newly learned information over time. Loring perceives potential problems arising from the comparison of GMI and DRI because the two scores are not directly comparable due to the different composition and weighting of the subtests entering each index.

There is no delay condition for Figural Memory, but performance on that task is included in the Visual Memory and, subsequently, in the General Memory Index. Further, the same subtests are weighted differently for the GMI and the DRI, e.g., the weight for Logical Memory on the Verbal Memory Index (the weight reflected in the GMI) is 2, but the same subtest has a weight of 1 in the DRI; Visual and Verbal Paired Associates are weighted 1 in the immediate recall indexes, but weighted 2 in the DRI.

Loring (1989) notes a further difficulty with the delayed measures; prompting is allowed for Logical Memory II, but not for Visual Reproduction II. He argues that the failure to allow a prompt for Visual Reproduction II has the potential of introducing "significant variability in performance" (p. 65) and points out that if a patient is unable to recall the fourth design, that patient loses 43% of the possible points for Visual Reproduction II.

A number of suggestions for improving delayed recall are offered in Loring's 1989 review of the WMS-R. He suggests that it is preferable to examine memory decay through difference scores. This approach would require that delay for the paired-associate subtests be measured against the number of items recalled on the final trial of acquisition rather than against total learning as is the case with the current scoring procedure. Logical Memory and Visual Reproduction are not problematic in this respect as the same number of raw score points is available for both immediate and delayed recall. With these changes, the same metric could be applied for all subtests entering the Delayed Recall Index. Loring also suggests that a multiple choice paradigm for Visual Reproduction II would allow "examination of memory for designs over time without confounding retention with free-recall failure" (1989, p. 65). Such a change would, however, have the result that delayed recall of Logical Memory II would measure, with the prompt or cues, cued-delayed recall while Visual Reproduction II would measure visual recognition. Both cued-delayed recall and recognition are measures of retention, but certainly not the same measure of retention.

Scoring Criteria

Loring (1989) declares that the scoring criteria "have been improved significantly" and that the improvements will produce greater scoring reliability. He acknowledges some disagreements with some of the criteria for scoring the Logical Memory subtest on the basis of personal biases, but he does not consider the scoring criteria for Visual Reproduction.

Significantly difficulties with the criteria for Visual Reproduction appear to remain. Delis et al. (1992) demonstrated that AD and cerebral vascular accident (CVA) patients may be differentially impaired on local (detail) and global (configural) forms. When presented with "hierarchical stimuli consisting of a large (global) form made up of smaller (local) forms" (p. 464), patients with left CVAs are selectively impaired in constructing local forms, while patients with right CVAs are selectively impaired in constructing global forms. The WMS-R scoring criteria for scoring Visual Reproduction are inconsistent with regard to local (detail) and global (configural) forms. For example, a single circle from Card B, arguably, a configural form, receives no credit, while on Card C another configural form, a large figure (though there is no criterion for 'large') "that is square in shape" (Wechsler, 1987, p.106) receives credit. In other cases, excellent recall of local form may receive no credit. A recent example from this investigator's clinical experience illustrates this point. A patient drew, in a square pattern, four "medium-sized squares", with four dots in each. That patient demonstrated obvious recall of local forms, but received no credit because according to scoring criterion Card C, 5. "One medium-sized, square-like figure is drawn in *each quadrant of the large square* [italics added]" (Wechsler, 1987, p. 107); hence, no large square, no credit. Similarly, from Card A, a patient drawing of two parallel staffs with two square flags on each, demonstrating retention of detail form, would receive no credit because the staffs did not cross, that is, he or she receives no credit because of loss of configural form. The same questions of local versus configural forms are relevant in the Figural Memory subtest. It is conceivable that two patients, one with right-hemisphere lesions and a second with right-hemisphere lesions, may receive the same score on Figural Memory. Successful recognition for the first patient may result from the ability to recall specific details

while the second is successful because he or she recalls a general configuration of lighter and darker patterns.

Review of the scoring criteria for Logical Memory and "examples of alternative 1-point responses" (Wechsler, 1987, pp. 95-100), and review of the scoring criteria for Visual Reproduction and "sample drawings that would *not* receive credit" (pp. 101-113) suggests that the scoring rules for Logical Memory are considerably more tolerant of "gist" than are the scoring rules for Visual Reproduction. That difference suggests that the comparison of verbal and visual memory with these measures is somewhat tentative at best.

Wechsler (1987) acknowledges the "relatively lower reliabilities and consequently larger SE_{β}s" (p. 63) of the Visual Memory Index, and recommends caution when interpreting the scores of that index. Given that Visual Reproduction contributes 41/69 points or 59% of the Visual Memory Index, scoring criteria that clearly and consistently reflect or require recall of configural form would likely contribute significantly to the Visual Memory Index as a measure of right-hemisphere function and, perhaps, to its reliability.

Factor Analytic Studies

Bornstein and Chelune (1988) undertook a number of factor analyses of the WMS-R with a large clinical sample (N=434). One analysis included only the immediate-recall subtests, another included immediate- and delayed-recall subtests, another included Verbal and Performance IQs with the immediate subtests, and yet another included IQs with both immediate- and delayed-recall subtests. Comparisons were made between the clinical sample and the WMS-R standardization sample for the first two of these.

The initial analysis, using Principal Components factor analysis, with the eight immediate-recall subtests yielded a two factor solution for both the standardization and clinical groups. The strongest loadings on factor I, interpreted as a general memory factor, were, for both groups, Logical memory, Visual Reproduction, Verbal Paired-Associate and Visual Paired-Associate Learning. The strongest loadings on factor II, interpreted as an attentional factor, were from Digit Span, Visual Memory Span, and the Mental Control subtests. In the clinical sample, Figural Memory and Logical Memory loaded

more strongly on the general memory factor while in the standardization sample the two subtests loaded more equally between the two factors. Visual Memory Span loaded, conversely, on both factors in the clinical sample but primarily on the attentional factor for the standardization group.

The addition of IQ scores to the subtests analysis yielded results that are not precisely comparable as Full Scale IQ (FSIQ) was measured with the standardization sample while Bornstein and Chelune used VIQ and PIQ scores for the clinical group. With the normal sample, FSIQ loaded on the attentional factor, and that factor was the first factor extracted. VIQ and PIQ scores also loaded on the attentional factor with the clinical group, but in that analysis, the attentional factor was the second factor extracted. General Memory was the first factor extracted.

In their next analysis, Bornstein and Chelune included all of the subtests, immediate- and delayed-recall, with the clinical group only. In that analysis, two strong factors emerged, a verbal memory factor (Logical memory, immediate- and delayed-recall and Verbal Paired Associates, immediate and delayed) and a nonverbal memory factor (Figural Memory; Visual Reproduction, immediate and delayed; Visual Paired Associates, immediate and delayed; and Visual Memory Span). A third, weaker, attentional factor also emerged (Mental Control, Digit Span, and Visual Memory Span).

The final analysis with the clinical group added VIQ and PIQ scores to the all of the WMS-R subtests. The same three factors emerged with both IQ scores loading on the attention factor.

In another set of factor analyses, Bornstein and Chelune (1989) examined the factor structure of the WMS-R as a function of age and education for the same mixed clinical group. Analyses examining the influence of age on the WMS-R were undertaken for three age groups, ≤39 years, 40-55 years, and ≥56. With the youngest group two factors with eigenvalues greater than 1.00 emerged. The first factor loaded on Logical Memory, Verbal and Visual Paired Associates, both immediate- and delayed-recall subtests, while the second factor loaded on Visual Reproduction, immediate and delayed, and Figural Memory, subtests usually described as nonverbal, as well as those frequently associated with an attention/concentration factor, Mental Control, Digit Span, and Visual Memory Span. Factors I and II accounted for 56.4% of the variance. Two other factors with eigenvalues between .97 and 1.00 were found, but those

factors were not described. Analysis of the 40-55 years groups produced a similar two factor solution that accounted for 66.4% of the variance. A weak, but again unidentified, third factor with an eigenvalue of .90 also emerged. The oldest group produced a result very similar to that obtained with the middle age group.

When Bornstein and Chelune added VIQs and PIQs to the analyses, four factors with eigenvalues greater that 1.00 were found for the youngest group, but the factor structure for the two older groups was unchanged with IQ scores loading on the attention factor. In the ≤39 years group, the first factor loaded on the nonverbal tasks, with the exception of Visual Paired Associates, and on PIQ; the second on VIQ and attentional tasks; the third was a verbal memory factor; and the fourth was a learning factor which consisted of Visual and Verbal Paired Associates, immediate and delayed. The four factors accounted for 71.3% of the variance.

Bornstein and Chelune (1989) divided their sample into three educational groups, <12 years, 12 years, and >12 years. Analysis of the first two groups yielded two factor solutions (memory/learning and attention) with a weak and unidentified third factor. A three factor solution was obtained for the >12 years educational group with the emergence of a nonverbal factor. When IQ scores were added, a three factor solution, verbal, nonverbal, and attention, was obtained for all three groups, though the groups differed on the factor that emerged first. These findings contrast with those obtained in the Wechsler Manual (1987) of the analysis of education on factor structure. That research found no difference for educational and age groups. Bornstein and Chelune (1989) consider that the difference may have arisen due to difference in data entered into the analysis, e.g., the Wechsler research did not include IQ scores in the analysis of education, and differences in group composition, e.g., Bornstein and Chelune report that their youngest group "probably" had a greater proportion of seizure disorder patients and that the oldest group likely had a greater predominance of dementia and pseudodementia.

The third and fourth factors found in Bornstein and Chelune's (1988) analyses did not emerge in factor analyses undertaken by Wechsler's group. The WMS-R manual reports studies for the standardization sample and a mixed clinical sample (N=346) (Wechsler, 1987, pp. 75-77) which included the eight immediate-recall subtests and FSIQs. Those studies produced, using the same

factor analytic technique, the same two factors, general memory/learning and attention/concentration as were found by Bornstein and Chelune with the same subtests, but other analyses by the Wechsler groups found no other factors. The WMS-R manual asserts, but does not provide values to support, that when 12 subtests were used, all the delay measures loaded on the same two factors as their immediate-recall counterpart. Roid, Prifitera and Ledbetter (1988) performed a confirmatory factor analysis using a microcomputer version of LISREL with normal (N=316) and clinical (N=343) subjects and found the "best fit" was for a two factor model of general memory and attention/ concentration. They did not, however, included the delayed-recall subtests in their analysis. Their rationale for exclusion of the delayed-recall measures was reference to the WMS-R manual report that the delayed-recall measures loaded on the same factors as their immediate recall counterparts.

The failure of factor analytic studies to consistently find a visual, or nonverbal, memory factor or a factor reflecting delayed recall for normal samples would appear to suggest that the changes incorporated in the WMS-R have not advanced it beyond the WMS as a measure of memory function or, alternatively, that, among normal individuals, there are no modality differences in memory. The alternative is counter-intuitive. Measures of general cognitive function, IQ scores, demonstrate that there are measurable differences between verbal and nonverbal abilities. Further, clinical observation and lesion studies demonstrate that verbal and visual, or nonverbal, memory may be differentially impaired depending on the site of the lesion.

Factor analyses of mixed clinical groups do little to clarify the factor structure as the groups are rarely comparable. In Bornstein and Chelune's (1988) study nearly one-quarter of the patients, 106/434, were seizure disorder patients while there were about half that number, 58/346, in the smaller Wechsler mixed clinical sample. The Wechsler sample lists AD (N=24) and Dementia (N=18) separately while Bornstein and Chelune list only dementia (N=64). Bornstein and Chelune list nine disorders for their mixed clinical group with numbers in each group ranging from a maximum of 106 to a minimum of 20 and "numerous other diagnoses" for which no numbers are provided. The Wechsler studies list 14 separate diagnoses with numbers ranging from 62 to 8. A number of the disorders/diagnoses listed, seizure disorders, head injury,

tumor, stroke, aneurysm/arteriovenous malformation, brain cancer, yield different patterns of cognitive impairment depending on the brain area most affected, and there is no breakdown in either study of the proportion of left- and right-hemisphere cases. The balance of left-hemisphere and right-hemisphere cases may have implications for the emergence of a nonverbal memory factor.

Concluding Remarks on the Overview of the WMS-R

Loring (1989) concludes that the "WMS-R still appears to be more a test of verbal learning" (p. 67). That view appears to be supported by most of the factor analytic studies.

Loring is particularly concerned with the relative contributions of the subtests to the General Memory and Delayed Memory Indexes and argues that it is "essential to have immediate/delay *difference estimates* [italics added] for individual subtests since all measures will not be equally sensitive to memory dysfunction, and different relative contributions of the subtests comprise the General and Delayed Memory Indexes" (p. 67) He is also critical of the nonverbal measures and suggests that they "do not appear to be pure measures of visual learning/memory" (p. 67).

Supporting Loring's contention that the WMS-R changes have failed to incorporate conceptual advances made in cognitive, experimental and clinical psychology since the inception of the WMS, this investigator has identified difficulties with the structure of and evaluation of performance on the new visual/nonverbal subtests. Those difficulties include the observations that the Visual and Verbal Paired Associates subtests are not, strictly speaking, analogous because the Visual Paired Associates subtest has no "easy" items, and that the test designers failed to consider global and local forms in the design and scoring of the Figural Memory and Visual Reproduction subtests.

Loring (1989) concludes his review with this comment: "There exists unquestioned improvement in the test's 'surface structure.' However, the test's 'deep structure,' the area of more theoretical importance and interest, remains essentially unchanged" (p. 67).

THE WMS-R: PATTERNS OF PERFORMANCE

IQ-Memory Discrepancies

Bornstein, Chelune, and Prifitera (1989) examined the potential clinical utility of IQ-memory discrepancies in differentiating normal and clinical groups. Using a subset of 192 patients from the large clinical sample used in the factor analytic studies described above (Bornstein & Chelune, 1988) and 110 cases from two groups in the standardization sample of the WMS-R, Bornstein et al. (1989) examined discrepancies between WAIS-R IQs and the WMS-R performance. The principal diagnosis for approximately one-half of the clinical sample was epilepsy of which approximately 70% had temporal lobe seizure foci. The second major group in the clinical group was 64 dementia cases of which "most" were presumed DAT. The mean age of the clinical sample was 41.8 years (SD = 19.5). The normal sample included 55 cases from each of the 35-44-year-old and 65-69-year-old groups from the standardization sample.

Bornstein et al. found that the groups did not differ significantly on either VIQ-Verbal Memory Index (VbMI) or PIQ-Visual Memory Index (VsMI) discrepancies. When they further investigated the distribution of scores by three magnitudes of discrepancy, 12 points suggested by Milner (1975, cited in Bornstein et al., 1989), a discrepancy score equal to the mean plus 1 SD of the control sample (approximately 15 points), and a discrepancy score that 5% or fewer of the normal sample met (approximately 22 points). Their findings were that the Verbal and Visual Memory Indexes were not useful in documenting IQ-memory discrepancies between normal and clinical samples.

Bornstein et al. (1989) then contrasted FSIQ and Delayed Memory Indexes (DMI) discrepancies between the normal and clinical groups. That comparison yielded significant difference ($p < .01$) between the two groups. Using Milner's (1975) criteria, 18.2% of normals and 36.6% of patients had discrepancy scores greater than 12. When the mean (for the normal sample) plus 1 SD was used, 10% of the controls and 32.5% of the clinical sample had discrepancy scores greater than 15 points. At the 95th percentile, 5.5% of controls and 18.8% of patients had scores exceeding 22 points.

Inspection of the major diagnostic group (epilepsy) revealed that 32 patients had left temporal foci and 36 had right temporal foci. The right temporal foci group had a mean FSIQ-DMI discrepancy score of 7.3 (SD 15.5) and

the mean FSIQ-DMI discrepancy for the left temporal foci group was 5.1 (SD 12.9). The group with presumed DAT had the greatest FSIQ-DMI discrepancy score: mean 16.0 (SD 15.1).

It is interesting to observe with regard to the Bornstein et al. (1989) study that from the perspective of clinical psychology, one could not make the case that the clinical sample showed memory impairment relative to overall clinical impairment. At the 95% level of confidence, the ranges of standard of error of measurement for both the WAIS-R and WMS-R show considerable overlap. With regard to the epilepsy group and the FSIQ-DMI discrepancies, the 95% level of confidence for the 35-44-year-old age group for FSIQ is ±4 and ±13 for the DMI. Given that the purpose of the study was to examine the clinical utility of the discrepancy scores, one can argue that discrepancies of 7.3 and 5.1 points have no clinical utility. Even the 16 point discrepancy found for the presumed DAT group is suspect inasmuch as the 95% level of confidence for the 65-69-year-old group is ±4 for FSIQ and ±14 for DMI.

Saving Scores

Cullum, Butters, Tröster and Salmon (1990) found that the severity and patterns of losses differentiated normal aging from "abnormal" forgetting. They suggest that extremely low "saving scores" or percent retention (delayed recall/immediate recall X 100) differentiate DAT patients from individuals experiencing normal age-related memory decline. In a previous paper (Butters et al. cited in Cullum et al., 1990) it was found that saving scores for DAT patients were 20% for Visual Reproduction and 15% for Logical Memory. In their 1990 paper, Cullum et al. report saving scores for a sample of normal elders (75-95 years) of 83% for Logical Memory and 68% for Visual Reproduction. They commented on the pattern difference; the normal elderly demonstrate better savings on Logical Memory while the DAT patients in the previous study showed better savings on Visual Reproduction.

An older study by Brinkman, Largen, Gerganoff, and Pomara (1983) obtained similar results. Brinkman et al. refer to the instrument used as the WMS-R throughout their paper, but they, in fact, used the RWMS, Russell's (1975) Revision of the WMS. Twenty-five DAT patients were matched for age and education with normal group of 31 elders (55-85 years) living independently in the community. The percent retention scores for Logical Memory were 24.40%

and 75.30% for the DAT and control groups respectively, and 37.94% (DAT) and 77.31% (NC) for Visual Reproduction. In their study, the pattern of differences found by Cullum et al. (1990) were not evident. Brinkman et al. found that both groups showed better savings for Visual Reproduction than for Logical Memory. The pattern difference between the two studies may be a result of the changes made in the Logical Memory and Visual Reproduction subtests in the revision of WMS to the WMS-R, that is, the substitution of a new Story B in Logical Memory and, in the Visual Reproduction subtest, the addition of the circular figure as Card 2, the deletion of the WMS Card 3 with two linear figures, and substitution of Card 4 with one linear and one circular figure. This is, however, a somewhat tentative argument as a study by Jacobs, Tröster, Butters, Salmon, and Cermak (1990) demonstrated that the new Visual Reproduction figures of the WMS-R evoke fewer intrusion errors in DAT patients than do the WMS figures, and more intrusion errors should lead to lower Visual Reproduction scores for DAT groups. Further, the WMS-R figures were administered, on the average, approximately 7 months after the WMS figures.

Differentiation of Demented, Amnesic and Normal Controls with the WMS-R

Butters et al. (1988) administered the WMS-R to amnesic, DAT, and Huntington's Disease patients and normal controls. Performances on the Memory Indexes were reported first. DAT patients performed significantly more poorly than either amnesic patients or normal controls on the Attention/Concentration Index. On the Verbal Memory Index, DAT patients' scores were significantly lower than either normal controls or amnesic patients. DAT patients performed significantly more poorly than normal controls on the Visual Memory Index, and DAT patients performed more poorly than amnesic subjects (mean Visual Index 69.85 and 78.31, respectively) but significance is not reported. DAT patients acquired lower scores on the General Memory Index than normal controls and amnesic patients and the differences were significant. On the Delayed Memory Index, DAT patients performed significantly below the normal controls, but better, though not significantly so, than the amnesic patients. The mean Delayed Memory Index was 60.70 for DAT patients and 56.63 for amnesic subjects.

Examination of difference scores produced the following results. The difference score between the Attention/Concentration and General Memory Index was significant between DAT and normal controls and between DAT and amnesic patients though in the opposite direction; the DAT patients had a greater difference score than normal controls, but a smaller difference score than amnesic patients. The difference score between the General Memory Index and Delayed Memory Index was significantly greater for amnesiacs compared to every other subject group; the difference score between DAT patients and normal controls was not significant.

Butters et al. (1988) also compared savings scores among the groups. On Logical Memory savings, the normal controls "saved" significantly more than both the DAT and amnesic groups, and while the savings scores for the DAT group were greater than the amnesic group (15% and 9%, respectively) the significance is not reported. Analysis of variance for Visual Reproduction yielded significant main group effects. The normal controls obtained higher savings scores than either DAT or amnesic patients on Visual Reproduction. Level of significance for differences between DAT and amnesic patients is not reported, but the savings difference between old normal controls and DAT patients was 5 percentage points and the difference between DAT and amnesic patients was 30 percentage points with the DAT group having the greater savings. While it is not discussed, it is likely that floor effects played a role in these results. It is noted that "one or two patients" in each group were excluded from the analysis because they scored zero on immediate recall. There was no significant group effect for savings scores on Visual Paired Associates. On Verbal Paired Associates there was again no significant main effect for groups, but pairwise *t* tests revealed a marginally significant difference ($p < .05$) between old controls and amnesic patients.

Butters et al. (1988) state that the findings of their study offer substantial evidence that the WMS-R is superior to the WMS, and that the WMS-R can distinguish amnesic disorders from some forms of cortical and subcortical dementias. They suggest that the difference between the Attention/ Concentration Index and General Memory Index may assist in estimating the degree of overall intellectual impairment, and that saving scores which reflect the rate of forgetting "may be one of the most valuable clinical

measures derived from the WMS-R" (p. 145). Butters et. al. do, however, find some difficulties with the WMS-R. They note that in their study more than 25% of the demented and amnesic patients earned scores below 50 on the General and Delayed Memory Index, and "Since the current standardization of the WMS-R does not allow the awarding of scores below 50, some patients' memory indices remain somewhat inflated and may not constitute a fully accurate reflection of the severity of their anterograde amnesia" (Butters et al., 1988, p. 146). The second major difficulty noted is the failure of the test makers to provide recognition tests for Logical Memory and Visual Reproduction. That omission precludes the direct comparison of recall and recognition memory and suggest that the "exclusion may limit the capacity of the WMS-R to differentiate among patients populations" (Butters et. al., 1988, p. 146).

WMS-R Patterns and Unilateral Lesions

Chelune and Bornstein (1988) investigated memory function in 115 patients with well lateralized right- and left-hemisphere lesions with the WMS-R. Multivariate analysis of the summary indices demonstrated a significant group effect, but subsequent univariate analysis showed that the groups differed from each other only on the Verbal Memory Index ($p < .009$). Univariate analysis of the subtests yielded significant group differences on Logical Memory I and II, and on Verbal Paired Associates I and II. The performance of patients with left-hemisphere lesions on each of these subtests was inferior to the right-hemisphere group. The reverse pattern, i.e., better performance by the left-hemisphere group on nonverbal/visual subtests, did not emerge.

Modality-specific retention was examined by saving scores or percent retention between Logical Memory I and II and Visual Reproduction I and II. Single group comparisons of percent retention Logical Memory and percent retention Visual Reproduction did not reveal significant differences. Chelune and Bornstein found, however, a significant ($p < .023$) interaction effect with a 2x2 Group (Right vs. Left) by Modality (Verbal vs. Visual) repeated measures ANOVA. The interaction demonstrated that right-hemisphere patients retained more verbal or semantic information than nonverbal/visual information while left-hemisphere patients showed the reverse pattern.

Chelune and Bornstein (1988) conclude "The results of the present study provide strong, albeit preliminary, support for the validity of the new WMS-R as a measure of modality-specific memory deficits. Some caution should be exercised in evaluating this study. As with the study by Bornstein et al. (1989), the patient group had low FSIQ's (left-hemisphere patients = 88.42; right-hemisphere patients = 85.64) and the FSIQ do not differ significantly from memory scores when the standard errors of measurement are considered. So, again, from a clinical perspective, the patient groups are better described as having general cognitive impairment rather than specific memory impairment. It is interesting, as well, that Chelune and Bornstein have chosen to report only FSIQs in this study when VIQs and PIQs seem more relevant to understanding the interaction of hemispheric lesions with various cognitive and memory demands.

Loring, Lee, Martin and Meador (1989) also investigated the impact of unilateral hemispheric lesions on WMS-R performance. They examined the clinical utility of the WMS-R in predicting the laterality of previous right and left temporal lobectomies. The performance of two groups, left temporal lobectomies (LTL) and right temporal lobectomies (RTL), was compared. The FSIQs of the LTL group, (88.5) were very similar to those in Chelune and Bornstein's left hemisphere group (88.42) while the Loring et al. RTL group had somewhat higher FSIQs (94.5 vs. 85.64). Loring and his colleagues used three index discrepancy criteria to classify patient performance. The first two, 16- and 21-point discrepancies, are from the WMS-R manual and represent the levels of statistical significance for difference between the Verbal and Visual Memory Indexes at the 15% and 5% levels of confidence. The third criterion was derived from a formula by Payne and Jones (1957 cited in Loring et al., 1989) which determined that on the basis of the standard deviation of difference scores and the average correlation of .5 between the Verbal and Visual Memory Indexes a 29-point difference was required for the 95% level of confidence.

Using those criteria, Loring et al. found, using the 16-point criteria, that 5/13 LTL patients had a lower Verbal Memory Index, which was consistent with left temporal lobe dysfunction. However, of the 11/20 RTL patients whose discrepancy scores exceeded 16 points, the Verbal Memory Index was lower which incorrectly suggested impairment of the left temporal lobe. Similar results

were obtained using the 21-point criteria. Four of 13 LTL patients exceeded the 21 point criterion, and all were correctly classified. Six of 20 RTL patients had difference scores equal to or greater than 21 points. Of those, only one was correctly classified; six had lower scores on the verbal index. Two LTL patients and two RTL patients had discrepancies that exceeded the 29-point criteria. Three of those were correctly classified, but one RTL patient was classified incorrectly. Loring et al. report that an additional two RTL patients had difference scores of 28 points, and both of those were incorrectly classified.

Loring et al. (1989) state "This report illustrates that relying solely on the WMS-R Verbal and Visual Indexes to infer lateralized temporal lobe dysfunction will lead to incorrect conclusions at an unsatisfactorily high rate" (p. 200), and they point out that with even the most conservative criteria, one-quarter of the patients were misclassified. Loring et al. observe, with regard to the Verbal and Visual Memory Index, that the "use of 'verbal' and 'visual' labels for the memory indexes . . . creates confusion between 'modality-specific' memory functions and 'material-specific' memory function. Verbal memory may be assessed through either the visual or auditory modalities." and "to the extent that language organizes thought, the labels 'verbal' and 'visuospatial' (or even 'nonverbal') would have been preferable" (pp. 200-201).

Summary of WMS-R Patterns of Performance

The literature reviewed indicates that VIQ-Verbal Memory Index difference and PIQ-Visual Memory difference are not useful measures for discriminating normal and clinical groups. FSIQ-Delayed Memory differences between clinical and normal groups reached significance, but, at best, with that measure only 10% of controls and 32.5% exceeded the cutoff selected. When saving scores or percent retention are used to assess rates of forgetting between normals and clinical groups, significant differences were obtained with clinical groups consistently showing lower saving scores. In another study DAT patients performed significantly more poorly than normal elderly controls on all the indices of the WMS-R, and in some cases, the indices differentiated between DAT patients and amnesic patients. Examination of the utility of the WMS-R in identifying the laterality of hemispheric lesions

yields mixed results. On the whole, that research suggests that the verbal subtests identify left-hemisphere lesions with some consistency, but that performance on the visual or nonverbal subtests does not consistently identify right-hemisphere lesions, and with even the most stringent criteria, as many as one-quarter of right hemisphere cases are misclassified as left hemisphere lesions.

It is clear that performance on the WMS-R measures reflects more than retention. Only a few of the measures, personal information questions in the Information and Orientation subtest, and counting, adding, and knowledge of the alphabet in the Mental Control subtest, demand recall of "old" learning or learning that is not periodically "updated". All other measures demand new learning. Learning makes demands on many different cognitive processes and learning through different modalities makes greater demands on some cognitive processes than others. An analysis of the cognitive demands made by each subtest might provide insight into the performance of various clinical groups on the subtests, and it is to that task that this investigation now turns.

ANALYSIS OF THE WECHSLER MEMORY SCALE--REVISED SUBTESTS

In contrast to the Wechsler Intelligence Scales whose subtests have been extensively analyzed in terms of their cognitive demands (Bannatyne, 1974; Kaufman, 1979; Sattler, 1982), task analysis of the Wechsler Memory Scales has been largely ignored. An understanding of the unique cognitive demands of each subtest will contribute to the interpretation of the patterns of performance of different clinical groups on the WMS-R and, potentially, assist in differential diagnosis.

The analysis is an initial, perhaps halting, effort and may be found wanting. It may, however, stimulate reaction and comment that will lead to a better understanding of precisely what the WMS-R subtests are and are not measuring. The analysis also defines the dependent variables in this investigation. The analysis comments on the content, task(s), basic cognitive abilities (and in some cases additional facilitative cognitive abilities), memory requirements, and factors contributing deficit performance.

Content Analysis

Content analysis describes the nature of the stimulus material, e.g., personal information, abstract designs, orally presented narratives, etc., and the classification of the content relative to certain memory constructs, e.g., episodic, semantic, verbal, visual or figural. The memory constructs are described under Memory Requirements.

Task Analysis

Task analysis identifies what is to be done with the content, e.g., recalled, learned, retained, and the response required.

Basic Cognitive Abilities

Psychologists have had little success in agreeing on the number of cognitive skills and abilities that make up human intelligence, and it is not the purpose of this analysis to enter that fray. The cognitive requirements described are those which clinical practice, research, and reasonable assumption based on research and clinical observation suggest are basic to successful performance of the tasks described. In each case, many other cognitive abilities will impinge on performance, but those delineated are believed to have particular relevance to performance of the task specified, and no claim is made that the list of abilities for each task is exhaustive. In some cases, abilities that are considered to be facilitative of, but not essential to, good performance are included as separate entries.

Memory Requirements

Memory requirements describe means of retrieval, the classification of the information to be retrieved, e.g., declarative, semantic, verbal, and the "buffer" from which the information is to be retrieved, i.e., immediate or primary, long-term or secondary, and remote or tertiary.

Following Erickson's (1990) definition, declarative memory is contrasted with procedural memory and is considered, in the analysis, to subsume both semantic and episodic memory. For this discussion "Declarative memory pertains to facts about the world and past personal events that must be *consciously retrieved to be remembered* [italics added]" (Erickson, 1990, p.

160). Procedural memory is involved in learning skills and procedures; retrieval is relatively automatic and does not require conscious effort. Semantic memory is relatively context free and "includes organized knowledge regarding words, concepts and their associations, and rules for manipulating these symbols and concepts" (Nebes et al., 1984, p. 321); it is "in essence our knowledge of the world" and is "acquired early, is overlearned, and is resistant to degradation" (Chertkow & Bub, 1990, p. 397). Chertkow and Bub (1990) identify episodic memory and semantic memory as separate subcategories within long-term memory, but Knotek et al. (1990) identify episodic memory as a subsystem of semantic memory. For this investigation, a definition with an example offered by Nebes et al. (1984) is selected: "Episodic memory is an autobiographical record of unique episodes and events in an individual's experience, encoded and maintained in relation to a particular temporal-spatial context . . . Thus a person's recollection of seeing a canary in a shop window the preceding week or of hearing the word *canary* among a list of 20 words given an hour earlier in a memory study, involves episodic memory" (p. 321).

The analysis use of the terms *declarative* or *procedural* indicate, respectively, conscious retrieval information or the relatively automatic evocation of learned processes or operations. The terms *semantic* or *episodic* reflect the source of the information. The terms *verbal* and *figural* (and visual) indicate, following Loring et al. (1989), the 'material-specific' memory function. Memory "buffers" or "stores" (primary, secondary and tertiary) are, following the parameters established in an earlier chapter, designated *immediate, long-term,* and *remote.*

Factors Contributing to Deficit Performance

Performance on all subtests will be impaired in some circumstances, for example, in delirium and moderate to severe dementia. It is not likely that a clinician would knowingly administer a memory battery to a delirious patient; however, the same clinician may very well administer a memory battery to a dementing patient. The list of factors contributing to deficit performance does not include disorders or conditions, like delirium, in which a memory battery would not typically be administered but will attempt to include

disorders and conditions a clinical psychologist might encounter. The list is meant to be illustrative rather than exhaustive.

The complete analysis is presented in *Appendix 1 Content and Task Analysis of the Wechsler Memory Scale--Revised Subtests.*

The analysis suggests that the WMS-R is in large measure an instrument that measures learning to a much greater extent than it does memory. The analysis also suggests, in the relative amounts of space required to discuss Basic Cognitive Requirements and Memory Requirements between the immediate- and delayed-recall subtests, that the primary measures of memory, *per se*, are the delayed-recall subtests, or, more precisely, the difference or saving scores between immediate and delayed recall. That suggestion is supported by the research findings already discussed; the most sensitive measures in discriminating between normal and impaired groups are the Delayed Recall Index and the savings scores.

If the WMS-R is primarily a measure of learning, is it, then, a potentially useful instrument in the differential diagnosis of dementia of an Alzheimer's type? The answer is "Yes". Dementia includes, but is not limited to, memory impairment. By definition, dementia requires impairment of other higher order cognitive functions. Failure to recall or retain information may reflect a memory disorder, but such failure may also reflect, as a number of cognitive psychologists have pointed out, a failure to acquire information. Butters et al. (1988) demonstrated significant difference between amnestic and DAT patients on the difference scores between the Attention/Concentration-General Memory Index and between the General Memory and Delayed Memory Index. The amnesic patients scored better than DAT patients on the Attention/ Concentration Index, but more poorly than the DAT patients on the General Memory Index. Further, the amnesic patients had greater difference scores between their General Memory Index and Delayed Memory Index than did DAT patients, despite the fact that DAT patients were more impaired (greater than 2 SD relative to the norms for normal subjects) on the Dementia Rating Scale. These results may be interpreted as reflecting not just memory impairment, but the impairment of multiple cognitive processes in DAT. It follows that an instrument that reflects the impairment of multiple cognitive processes as

well as memory is, potentially, a suitable instrument for contributing to the differential diagnosis of DAT.

Chapter Summary

The evolution of the Wechsler Memory Scale-Revised from the original Wechsler Memory Scale and Russell's Revised Wechsler Memory Scale was examined. The limitations of the original scale and the attempts of the revised instrument to removed those limitations through the increasing the number of scales, the inclusion of scaled scores for the scales, and the inclusion of several composite scores, rather than a single Memory Quotient, as well as attempts to improve the standardization and statistical properties of the scale were noted.

The strengths and weaknesses of the Wechsler Memory Scale--Revised were examined. The new subtests and scoring criteria were reviewed in some detail, and it was observed that while the Wechsler Memory Scale--Revised has limitations, it is an improvement on the original instrument. A number of the investigations of the revised scale's factor structure were reviewed as were studies examining some patterns of performance, e.g., IQ-memory discrepancies, savings scores, different clinical groups, on the revised instrument.

It was noted that unlike the Wechsler Intelligence Scales whose subtests have been subjected to extensive analysis, there does not appear to have been a similar analysis of the subtests of the Wechsler Memory Scale--Revised, and an initial analysis was offered.

CHAPTER 7
RESEARCH QUESTIONS AND HYPOTHESES

Chapters 4 and 5 have reviewed a number of papers that have demonstrated that there are quantitative differences between individuals with DAT and other groups (the normal elderly, elderly suffering benign senescent forgetfulness, MID, PD, HD, depression or pseudodementia, and some other disorders) in performance on a variety of psychometric instruments. Despite the differences in performances on a variety of instruments, authors cited throughout the review of literature have asserted that memory deficit is the "hallmark" of Alzheimer's disease. In Chapter 5, it was demonstrated that there are quantitative differences among individuals with AD, individuals with other dementias, and individuals who show only normal age related memory changes on a variety of instruments measuring, or purporting to measure, several facets or dimensions of memory. Many of those authors as well as many other researchers have underlined the importance of early detection if AD is to be treated or managed. A key element in early detection of AD is differential diagnosis, and, it is argued here, that patterns of memory change can make a substantial contribution to early differential diagnosis.

It is reasonable to suggest that a clinical memory "battery" which incorporates a variety of measures of different facets of memory could make a substantial contribution to the differential diagnosis of AD. There are a number of such "batteries", but the predominant instrument is the Wechsler Memory Scale (WMS)(Wechsler, 1945) and its revision, the Wechsler Memory Scale--Revised (WMS-R) (Wechsler, 1981). Both versions of the instrument were reviewed in detail in the Chapter 6 of this investigation. For the present, it will suffice to say that the revision, the WMS-R, with its greater number of subtests, is a better candidate for a memory battery that has the potential to make a significant contribution to the early differential diagnosis of AD than is its predecessor.

The question addressed in this study is "Can the Wechsler Memory Scale--Revised make a unique contribution to the differential diagnosis of Alzheimer's type dementia".

The WMS-R is comprised of 13 subtests and yields five indices, General Memory, Attention/Concentration, Verbal Memory, Visual Memory, and Delayed

Recall. The Verbal Memory Index is comprised of the weighted scores of the Logical Memory I and Verbal Paired Associates I subtests while the Visual Memory Index is derived from the Figural Memory, Visual Paired Associates I, and Visual Reproduction I subtests. The General Memory Index Composite, described as one of two major scores, includes all of these subtests but the index is derived by summing the weighted scores of the subtests included in the Verbal Memory Index and summing the weighted scores of the subtests included in Visual Memory, then adding the sums to obtain a General Memory Index. The second major score is the Attention/Concentration Index which is composed of the weighted scores of the Mental Control, Digit Span, and Visual Memory Span subtests. The Delayed Recall Index consists of the weighted scores of the Logical Memory II, Visual Paired Associates II, Verbal Paired Associates, and Visual Reproduction II subtests. One subtest, Information and Orientation Questions, is not included in any of the indices and is "intended primarily to identify persons for whom the meaning of scores on the rest of the scale may be questionable" (Wechsler, 1987, p. 51). Kerlinger (1973) states that in ex post facto research it is possible to set up and test alternative hypotheses. The structure of the WMS-R suggests the alternative hypotheses.

The alternative hypotheses to be tested in considering the question whether the WMS-R can make a unique contribution to the differential diagnosis of DAT are as follows: *(1) the pattern of quantitative differences among the General Memory, Attention/Concentration, Verbal Memory, Visual Memory, and Delayed Recall composite scores or indices of the WMS-R is not sufficiently sensitive to differentiate DAT from other memory disorders, but will differentiate DAT and other memory disorders from normal age-related memory change*, and *(2) the pattern of quantitative differences among the subtest scores of the WMS-R, or a subtest of those scores, is sufficiently sensitive to differentiate DAT from other memory disorders and from normal age-related memory changes.*

HYPOTHESIS 1

Hypothesis 1 which asserts that the pattern of quantitative differences among the General Memory, Attention/Concentration, Verbal Memory, Visual

Memory, and Delayed Recall composite scores or indices is not sufficiently sensitive to differentiate DAT from other memory disorders, but will differentiate DAT and other memory disorders from normal age-related memory change is, in part, supported in the existing literature cited in the manual for *The Wechsler Memory Scale--Revised* (Wechsler, 1987). It is assumed that normal age-related memory changes are reflected in the various age groups of the standardization sample. The five WMS-R indices for a mixed clinical sample of 346 patients with either suspected or documented memory impairment were compared with those of the nonimpaired standardization group. A MANOVA using the index scores as dependent variables indicated that the clinical sample had significantly lower scores on the WMS-R indices than did the standardization sample. More to the point, research with two demented groups, 18 patients with dementia of mixed or unclear etiology and 24 patients "diagnosed as having Alzheimer's disease" (p. 82) were compared with "the normal group", presumably an age appropriate sample of the standardization group, and with each other. Both clinical groups scored significantly (*ps* < .001) lower than the normal sample on the set of indices and on each index separately. Both clinical groups also scored significantly lower than the normal group on the Information and Orientation Questions; however, the mean for the non-Alzheimer dements on that subtest was less than 1 point lower than the mean of the normals. The DAT group scored significantly lower than the non-Alzheimer group on the General Memory, Verbal Memory, and Information and Orientation Questions, but it should be noted that the mean age of the DAT group was nine years older than the non-Alzheimer's group. The mean age of the DAT group was 67.9 years. To yield that mean age, the sample would have included both presenile and senile forms of Alzheimer's type dementia, and, given that the instrument is standardized to only 74 years 11 months, only a relatively young DAT sample could have been accurately compared to the normal sample. In fairness it should be noted that the review of studies cited in the manual concludes with the following remarks:

> Data on the clinical groups has been presented for purposes of establishing the criterion-related validity of the WMS-R. These data are not meant to be representative of these selected clinical groups but rather as illustrative and suggestive. Many other factors (e.g., length

> and severity of illness, age of onset, length of hospitalization, medications, diagnostic subtype) which were not controlled for in the results reported here may affect WMS-R scores. Nevertheless, these data do support the utility of the WMS-R in assessing memory impairment. Future research with larger samples, different clinical groups, and more exactly defined groups is needed to further understand how the WMS-R may be most useful in the assessment of memory impairment (Wechsler, 1987, p. 86).

The investigation undertaken here appears to be of the sort called for in the last sentence above.

The research cited in the WMS-R Manual (Wechsler, 1987) suggests that the indices of the WMS-R will likely differentiate pathological changes in memory from normal age-related memory change; however, none of the studies reported in the WMS-R manual address the question of whether the indices will make a contribution to the differentiation of Alzheimer's type dementia from other disorders of memory, especially at the early stages, when the groups are not all ready differentiated by other means.

HYPOTHESIS 2

Hypothesis 2 proposes that the pattern of quantitative differences among the subtest scores of the WMS-R, or a subset of those scores, is sufficiently sensitive to differentiate DAT from other memory disorders and from normal age-related memory changes. The review of literature for this investigation failed to identify any studies that have approached this question. Perhaps the absence of such studies should be a caution to this researcher; however, there are observations in studies of the WMS-R that do appear to suggest that the direction of this research is tenable.

Loring (1989) suggests that the use of summary measures, like the indices of the WMS-R, may be insensitive to the variety of performances displayed by patients with brain dysfunction because the "smoothing necessitated by collapsing scores obscures patterns that may be clinically relevant" (p. 61). This argument would appear to offer additional support to Hypothesis 1, but it also implies that there are patterns among the subtests of the WMS-R that may be clinically relevant for different groups of brain injured persons, and that implication can be taken to support Hypothesis 2.

Bornstein and Chelune (1989), who have authored a number of papers on the WMS-R (Bornstein, Chelune, & Prifitera, 1989; Bornstein & Chelune, 1988; Chelune & Bornstein, 1988) state in conclusion of a study on the WMS-R factor structure that "In the context of clinical issues it would be of value to compare patterns of memory deficit across diagnostic groups to determine if patterns of performance with specific diagnostic significance could be identified (e.g. depression vs. dementia). These patterns could be examined within the WMS-R alone or in the context of other neuropsychological data" (p. 23). They suggest that cluster analytic techniques could have theoretical and practical significance in such a pursuit.

The qualification that the diagnostically significant pattern among the subtests may arise only in a certain subset of those subtests arises from the expectation, suggested by factor analysis and elsewhere, that there is some redundancy among the subtests. Some subtests, then, may measure essentially the same facet of memory, though each may not measure with equal sensitivity; hence each of those subtests may not make a unique contribution to early differential diagnosis of DAT.

In summary, the question addressed is whether the WMS-R can make a unique contribution to the differential diagnosis of DAT. The hypotheses are (1) that while the pattern of quantitative differences of performance on the WMS-R Indices will differentiate DAT and other memory disorders from normal age-related memory changes, those indices are not sufficiently sensitive differentiate DAT from other memory disorders; and (2) the pattern of quantitative differences among the subtest scores of the WMS-R, or a subset of those scores, is sufficiently sensitive to differentiate DAT from other memory disorders and from normal age-related memory changes.

CHAPTER 8
METHODOLOGY

OVERVIEW

This research utilized the assessment records of 210 patients seen in a memory clinic and on assessment and rehabilitation units of a geriatric facility in a large urban area of Alberta. All patients included had received a careful medical examination and a comprehensive neuropsychological assessment that included the WMS-R.

For this study, patients were grouped by medical diagnosis, degree of impairment, and, indirectly, by age. An impairment index was derived from neuropsychological measures other than the WMS-R. The performance of patient groups on the WMS-R Indexes and subtests, other than the Information/ Orientation subtest, as well as two additional measures derived from subtest performance, was compared. The quantitative performances of the groups were analyzed to determine whether the WMS-R performance profiles of the various diagnostic groups were reliably different, and whether there is a characteristic WMS-R profile that identifies DAT patients, especially those at early stages of the disease. Statistical analyses included discriminant function analysis and cluster analysis.

The preceding paragraphs provide an overview of methodology of this investigation. The discussion now turns to a more detailed analysis of the subject group, instruments, procedures, and statistical analyses.

THE SAMPLE

The Edmonton General Hospital is a major geriatric facility in western Canada. The primary role of the Edmonton General is assessment and rehabilitation of geriatric patients. In addressing that role, the hospital provides a Geriatric Outpatient Clinic and a Memory Clinic in addition to the services provided on the inpatient assessment and rehabilitation units. Patients from all of these services are, at the discretion of the attending physician, referred to Psychological Services for assessment of memory and other neurocognitive disorders. Many of those patients have received a complete neuropsychological assessment which, over the last 3-4 years, has included the Wechsler Memory Scale--Revised.

The medical conditions/disorders with which those patients have presented are diverse but include probable Alzheimer's disease, multi-infarct dementias, mixed DAT and MID, depression, Parkinson's disease and other parkinsonian disorders, metabolic disorders, alcoholism and alcohol abuse, reactions to medications, closed head injury, and others. As the Memory Clinic was not restricted to geriatric patients (≥65 years), a number of younger patients, especially those with closed head injury, depression, and substance abuse problems have been seen. The vast majority of patients are, however, older than 65 years, and individuals in their 90s have been assessed.

Psychological assessment reports and medical records for 243 cases were recovered. Of those cases, 29 were second assessments of the same individual, and four were third assessments of the same individual. Follow up cases were excluded and 210 remained in the sample. Of the 210 cases, 125 were females and 85 were males.

The characteristics of the sample are summarized in Tables 8.1.a and 8.1b. Table 8.1a reports demographic, other than Occupational Level, and cognitive variables by total group, females, and males. Table 8.1b reports Occupation Level.

Age of Sample

The mean age of the group was 72.56 years with a standard deviation (*SD*) of 8.98 years. The mean age of the female cases was 73.80 (*SD* 8.35) years and the mean age of males was 70.74 (*SD* 9.58) years. The difference in age was significant (p = .0151). While the age difference is significant, in part due to the large sample size, both groups fall within the same WMS-R normative group, 70 -74 years.

Education

The mean educational level of the group was 10.07 (*SD* 3.77) years. The difference between the educational level of females and males at 10.12 years and 10.00 years, respectively, was not significant (p = .8505).

TABLE 8.1a

SAMPLE CHARACTERISTICS

Variable	Group Mean	(SD)	Females Mean	(SD)	Males Mean	(SD)	F	p
	(N = 210)		(N = 125)		(N = 85)			
Age	72.5599	(8.9753)	73.7982	(8.3528)	70.7419	(9.5821)	5.9993	.0151
Educ.	10.0714	(3.4447)	10.1200	(3.2169)	10.0000	(3.7733)	.0611	.8050
EVI	100.6381	(10.7362)	99.7360	(10.4466)	101.9647	(11.0771)	2.1927	.1402
EPI	101.7095	(7.6388)	101.3200	(7.4375)	102.2824	(7.9352)	.8023	.3715
EFI	101.4333	(9.7398)	100.7040	(9.7365)	102.1058	(9.8450)	2.1196	.1469
VeMI	39.4476	(18.4448)	39.8000	(18.2001)	38.9294	(18.8956)	.1122	.7379
	(N = 203)		(N = 120)		(N = 83)			
ViMI	34.5320	(12.7284)	35.5333	(12.4542)	33.0843	(13.0545)	1.8237	.1784
GMI	74.3153	(27.5050)	76.0667	(26.8539)	71.7831	(28.8648)	1.1911	.2764
	(N = 203)		(N = 119)		(N = 84)			
DRI	36.1232	(20.3336)	36.3109	(19.1726)	35.8571	(21.9891)	.0244	.8760
	(N = 186)		(N = 110)		(N = 76)			
ACI	50.8333	(12.3682)	51.3182	(11.0959)	50.1316	(14.0555)	.4124	.5216
	(N = 186)		(N = 109)		(N = 77)			
II	37.6767	(10.3795)	38.3033	(9.8987)	36.7897	(11.0293)	.9595	.3288

Educ. = Education, years; EVI = Estimated Premorbid Verbal IQ; EPI = Estimated Premorbid Performance IQ; EFI = Estimated Premorbid Full Scale IQ; VeMI = WMS-R Verbal Memory Index (raw score); ViMI = WMS-R Visual Memory Index (raw score); GMI = WMS-R General Memory Index (raw score); DRI = WMS-R Delayed Recall Index (raw score); ACI = WMS-R Attention/Concentration Index (raw score); II = Impairment Index (T-score)

Occupational Levels

The vast majority of subjects in this study could have been classified into Category 4, "previously employed but not now in labour force," but that would have contributed little to an accurate representation of the population. As classified, there was a significant difference (p = .00001) in occupational level between males and females. The greater differences were not, however, as might be expected, found in the higher levels of the scale. Females were somewhat better represented than males in the professional category--12.8% vs. 10.6%, while males were better represented in Category 2

TABLE 8.1b

OCCUPATIONAL LEVEL BY SEX

SEX	OCCUPATIONAL LEVEL Professional 1	2	3	4	5	Unskilled 6	Total
Females	16	31	1	7	59	11	125
Males	9	23	20	4	23	6	85
Total	25	54	21	11	82	17	210
Percent	11.9	25.7	10.0	5.2	39.0	8.1	100.0

Codes: 1 Professional and technical; 2 Managers, officials, proprietors, clerical and sales workers; 3 craftsmen and foremen (skilled workers); 4 previously employed, but not now in labour force; 5 operatives, service workers, farmers and farm managers (semi-skilled); 6 farm labours, farm foremen, and labours (unskilled) Barona & Chastain (1986)

(managers, officials, proprietors, etc.)--27.1% vs. 24.8%. The greatest differences were in Category 3 (skilled craftsmen and foremen) and Category 5 (semi-skilled). Only 0.8% of females were classified in Category 3 compared with 23.5% of the males. Homemakers were classified in Category 5 with the result that 47.2% of the females in the study fell into that category. Category 5 collected 27.1% of the males.

Estimated Premorbid IQ'S

Premorbid Verbal, Performance, and Full Scale IQ's were estimated using a formula derived from the WAIS-R standardization sample by Barona and Chastain (1986) All estimated IQ scores fell near the middle of the Average range (see Table 8.1a), and there were no significant differences between the female and male groups.

WMS-R Indices

Weighted raw score composites of the research sample were calculated for each of the General Memory, Attention/Concentration, Verbal Memory, Visual Memory, and Delayed Recall Indices. Table 8.2 compares the research sample means with those of the 70-74 years age group in WMS-R standardization sample. The standardization sample is not divided by sex.

Table 8.2 shows that the research group is, in terms of standard neuropsychological classification, within the Normal range, albeit the lower end of that range, on all but the Verbal Memory Index raw score composite.

Table 8.2

Means and Standard Deviations of Weighted Raw Score Composites of 70 -74 Years Age Group and Research Sample

Index	WMS-R Sample Mean (*SD*)	Research Sample Mean (*SD*)	Difference Standard Deviation[1]
General Memory	92.7 (23.5)	74.3 (27.5)	-0.78
Attention/Concentration	59.9 (12.5)	50.8 (12.4)	-0.73
Verbal Memory	58.7 (17.1)	39.4 (18.4)	-1.13
Visual Memory	38.5 (10.3)	34.5 (12.7)	-0.39
Delayed Recall	52.6 (17.4)	36.1 (20.3)	-0.95

[1] (Mean WMS-R - Mean Research)/ SD WMS-R

The research group's Verbal Memory score is in the Mildly Impaired range of the Normal 70-74 year-old cohort. WMS-R raw score composites could not be calculated for all subjects due to missing data. (See Table 8.1a for numbers for each index.) The differences between males and females are not significant.

INSTRUMENTS

The Wechsler Memory Scale--Revised

This investigation is concerned with the potential utility of the Wechsler Memory Scale--Revised in the differential diagnosis of DAT. That instrument was reviewed in detail in Chapter 6 and a detailed review will not be repeated here. It is argued here that the WMS-R's potential as an instrument that might yield a differential diagnosis between DAT and other dementias lies in its variety of subtests that reflect different facets of memory and learning.

It will be recalled that the WMS-R has, when the Information/ Orientation Questions are included, 13 subtests which yield five composite

scores or indices. The subtests measure, or proport to measure, primary auditory and visual attention/memory (Digit Span, Visual Memory Span); attention/concentration (Mental Control); short-term, or immediate, verbal and visual recall (Logical Memory I, Visual Reproduction I); immediate visual recognition (Figural Memory); learning and recall of verbal and visual conditional associations (Verbal Pairs Associates I, Visual Pairs Associates I); delayed verbal and visual recall (Logical Memory II, Visual Reproduction II); and delayed recall of verbal and visual conditional associations (Verbal Paired Associates II, Visual Paired Associates II). The composite scores or indices reflect immediate verbal memory, immediate visual memory, immediate "general memory" (a composite of immediate verbal and visual memory indices), "general" long-term or secondary memory (a visual and verbal delayed recall composite score), and attention/ concentration.

THE QUESTION OF THE IMPAIRMENT INDEX

A number of studies (Martin et al., 1986; Haxby, 1990, Capitani et al., 1990; Liston & La Rue, 1983a) have either suggested qualitative differences in performance measures of memory by degree of impairment or have yielded results that are difficult to interpret because the extent of impairment was not documented. An impairment index allows examination of patterns of performance on the WMS-R subtests by degree of impairment (or stage) and facilitates interpretation of the results obtained. The index, to avoid circularity, was derived from measures other than the WMS-R since it is the efficacy in detecting difference between diagnostic groups by degree of impairment that is investigated.

The question raised is whether the Impairment Index (II) measures something different than do the indices of the WMS-R. The Impairment Index provides, in effect, a summary score of a brief neuropsychological examination. The index includes measures of general ability, verbal and visual learning, verbal and visual memory, visual perceptual and visuo-constructional abilities, and mental control. The individual test and subtest results were recorded as age-scaled T-scores, and a mean (unweighted) T-score was calculated. The mean T-score is the value of the impairment index and the basis for classification as either normal to mild impairment (M) or moderate to severe impairment (M-S).

A strong correlation between the II and the WMS-R Indices was expected in the sample as both are measures of impairment and most individuals the sample are impaired. Correlations between the two WMS-R Indices that best serve as summary measures of memory impairment for that instrument, the General Memory Index (GMI) and the Delayed Recall Index (DRI), are to be expected. The correlation between the II and the GMI is .7549 which is significant at less than $p = .01$ (2-tailed) and the correlation between the II and the DRI is .7093, again significant at $p < .01$. These values suggest that approximately 57.0% of the variance in the GMI and 50.31% of the variance in the DRI is accounted for in the II, and that 43% and 49.7% of the variance, respectively, is not accounted for in that measure. Multiple regression with the II as the dependent variable and the GMI and Dri as independent variables yields a multiple r of .756 and an adjusted r squared of .567. Again, approximately 43% of the variance in not accounted for in the association.

To further examine the relation between the II and the memory indices, separate t-tests were calculated between each of the memory indices as T-scores and the II. The differences between the Visual Memory Index (ViMI) and the II and between the Attention/Concentration Index (ACI) are significant at $p < .0005$. The ViMI-II test yields $t = 11.176$ and the ACI-II test yields $t = 4.807$. The DRI-II test t is 2.745 (actual $p < .005$), and the GMI-II test yields $t = 2.549$ (actual $p < .01$) suggesting marginal significance given the large number of subjects. The Verbal Memory Index (VeMI)-II t-test is not significant at $t = 1.010$. Critical t in each case is $2.35 = {}_{99}t_{200}$.

A similarity of means between the II and the GMI might be expected as both are summary measures of verbal and nonverbal abilities, but the reason for the closeness of means of the II and the VeMI is not immediately apparent. Review of the II does not reveal an over-loading of measures reflecting verbal abilities. The II consists of five "verbal" tests--WAIS-R VIQ; CVLT Total, Trials 1-5; CVLT, Trial 5; CVLT, Long-delay free recall; and FAS--and five "nonverbal" measures--WAIS-R PIQ; RCFT, Copy; RCFT, Delayed Recall; HVOT; and TMT-A. The eleventh measure, Trail Making Test, Part B, demands both verbal and nonverbal abilities, but is primarily a measure of mental control. Since all measures are unweighted, verbal abilities including verbal memory, ought not to have disproportionate weight in the II. However, it may be argued that

within the verbal component of the II, verbal memory is over-selected by the three CVLT subtests and that the subtests selected do introduce some systematic variance which draws the means of the II and the VeMI together. A study of convergence and divergence between the WMS-R and the CVLT (Delis et al., 1988) does reveal strong correlations between the CVLT subtests selected and the VeMI. The correlations of the CVLT subtests with the VeMI are as follows: CVLT, Total Trials 1-5 .910; CVLT, Trial 5 .906; and CVLT, Long-delay Free Recall .876 (all significant at $p < .01$). However, the same subtests show correlations of equal or greater magnitude with the DRI: CVLT, Total Trials 1-5 .918; CVLT, Trial 5 .920; and CVLT, Long-delay Free Recall .927 (all significant at $p < .01$), and the difference in means between the II and the DRI is significant at $p < .005$. Therefore, while the possibility that the CVLT subtests introduce some systematic variance into the II that selects for verbal memory cannot be excluded, acknowledging that possibility raises the difficulty of why the same subtests do not select for the DRI with which they show slightly stronger correlations.

Despite revisions, the WMS-R, like the WMS, is described as primarily a measure of verbal memory, and the hypothesis is suggested that the association between the II and the VeMI arises because the VeMI, rather than the GMI, is the best summary measure of impairment for the WMS-R. It is, however, difficult to provide a criterion for the "best summary measure." The VeMI does not have better reliability that either the GMI or the DRI. Test-retest stability coefficients of the 70-74 year old group in the standardization sample are VeMI .84, GMI .86, and DRI .84. and consideration of standard errors of measurement shows the VeMI $SE_{\bar{x}}$ at 6.80 is marginally greater than the $SE_{\bar{x}}$ of the GMI at 6.39 (DRI $SE_{\bar{x}}$ = 6.91).

The II correlates significantly with both the GMI and DRI but, first, leaves, in the stronger case, approximately 43% of variance unexplained and, second, yields a difference in means between the II and the memory indices, other than the VeMI. The equality of the means of the II and the VeMI is acknowledged, but it is difficult to demonstrate that the equality arises because the II systematically selects for verbal memory. The position is taken that the II is a measure of general cognitive impairment and is

sufficiently different from the WMR-S indices to serve as an independent measure of impairment.

Impairment Index

As reported above, the literature concerning subtypes in DAT and the literature examining differences between rates of forgetting between impaired and normal individuals, it was noted that the results of a number of studies were confounded by the failure to account for or to report, or both, levels or degrees of impairment. To avoid that difficulty, an impairment index was calculated for each patient in this study. Because dementia affects, by definition, not only memory, but other higher cognitive functions, the impairment index reflects multiple cognitive processes.

Table 8.3 lists the instruments and/or subtests from which the Impairment Index was drawn and the rationale for inclusion of the particular test or subtest. The selection criterion for a test or subtest is that it measures, or is believed to measure, some cognitive ability of interest that is not uniquely measured by another subtest, and that it contributes to the breadth of abilities reflected in the index. The tests and subtests included in the Impairment Index are drawn from the following instruments: Wechsler Adult Intelligence Scale--Revised (WAIS-R)(Wechsler, 1981); California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987); Rey-Osterrieth Complex Figure Test (RCFT) (Rey-Osterrieth, 1944); Hooper Visual Organization Test (HVOT) (Hooper, 1958); Trail Making Test, Parts A and B (TMT-A, TMT-B)(Reitan, 1958); and FAS (Borkowski, Benton, & Spreen, 1967). All scores were expressed as age-adjusted T-scores. For tests or subtests in which impaired performance is expressed as positive standard deviations, e.g., TMT-A and TMT-B, or greater T-scores, e.g., HVOT, T-score scales were inverted.

The Impairment Index assigned to each patient was that patient's average unweighted age-adjusted T-score. Impairment Indices for 109 females and 77 males could be calculated. The Impairment Index mean for the group is 37.68 (*SD* 10.38). The Impairment Index for females and males, respectively, is 38.30 (*SD* 9.90) and 36.79 (*SD* 11.03). Converted to standard deviations from

Table 8.3

List of Tests/Subtests Comprising the Impairment Index

Test/Subtest	Ability Assessed
WAIS-R Verbal IQ	General verbal ability
WAIS-R Performance IQ	General nonverbal ability
CVLT Total, Trials 1-5	New verbal learning
CVLT Trial 5	Immediate verbal recall
CVLT Long-delay free recall	Long-term verbal recall
RCFT Copy trial	Visuoconstructional ability
RCFT Immediate recall	Immediate visual recall
RCFT Delayed recall	Long-term visual recall
HVOT	Visual synthesis
TMT-A	Visual attention & scanning
TMT-B	Complex visual attention & scanning

the mean (z-scores) the impairment levels are: (a) group -1.23 *SD*; (b) females -1.17 *SD*; and (c) males -1.32 *SD*. In terms of neuropsychological descriptors, the group as a whole, females, and males are in the Mildly Impaired range with no significant difference between sexes (p = .3286).

METHOD

It was originally proposed that patients would be sorted by medical diagnosis into the following groups: Possible/probable dementia of an Alzheimer's type (DAT), multi-infarct dementia (MID), mixed DAT and MID (MIX), depression or pseudodementia (D), and other diagnoses (O). It was anticipated, on the basis of prevalence estimates, that approximately 50% of the sample would be DAT patients.

A note on the use of the word 'dementia' is required. The label 'DAT'--dementia of an Alzheimer's type--should be understood in the context of this investigation to be a label identifying cases of possible or probable Alzheimer's disease, and with the early cases a true dementia as defined by the DSM-III-R or DSM-IV is not necessarily implied. Similarly, 'vascular dementia' or 'Vas. Dem.' identifies cases for which a cerebral vascular lesion

is demonstrated or suspected on the basis of medical history and/or clinical presentation, and for the mildly impaired (M) cases, a full dementia is not implied.

Review of medical records revealed that classifying patients on the basis of diagnoses made by physicians was untenable. Despite the fact that each patient who received a psychological assessment was referred by a medical doctor, frequently the results of the psychological assessment were not included in the discharge diagnoses, or the results were re-phrased, for example, "short-term memory dysfunction", "mild cognitive dysfunction with anxiety", "advancing cognitive dysfunction", and "organic brain syndrome with selective frontal deficits." Those records were searched beyond the discharge summaries for a more definitive diagnosis. Most medical discharge summaries, however, recapitulated the psychological impression and the decision was taken to base the diagnostic groupings on the psychological reports. Cross tabulation revealed a 98.7% ($p < .0001$) agreement between the psychological impression and the medical diagnosis in patient classification.

Patients were initially sorted by a broader range of diagnostic categories that those described above. Table 8.4 lists the initial categories and the numbers in each category. Initial categorization yielded a different distribution of numbers of patients by diagnosis than anticipated in the proposal. Approximately one-half the anticipated number (48/100) of patients with a diagnosis of possible/probable DAT were obtained with the inclusion of the "DAT plus" cases. The numbers of vascular dementia (initially described as MID) obtained approximated the number anticipated (35 vs. 40) as did the number of depressed patients (19 vs. 20). An unanticipated large group (n = 27) of patients with frontal deficits emerged, and it was determined that those numbers warranted including that group in further analyses. It is not clear why the anticipated number of DAT patients did not emerge when the medical records and psychological reports were reviewed. It is improbable that the incidence of DAT is lower in Alberta than in the rest of North America. One possible explanation is selection bias. It is hypothesized that in many of the more typical presentations of DAT, the attending physicians, most of whom have substantial geriatric experience, made their diagnoses on their own experience without benefit of neuropsychological assessment.

The initial categorization yielded 22 none-empty groups; division into normal to mild impairment (M) and moderate to severe impairment (M-S) would yield 44 groups with unacceptably low numbers in each cell or category. The diagnostic categories were recombined to yield fewer cells (categories). Figure 8.1 outlines the recombination of the original groups.

The initial recategorization "collapses" the DAT + 3, 4, 6, and 8 groups (9 cases) to DAT Plus. Vascular Dementia (Vas. Dem.) + 3, 4, 6, 7, and Vas. Dem + Other 29 (19 cases) form the Vas. Dem. Plus category. Other, Other Psychiatric, Metabolic/ETOH, Seizure Disorder, Parkinsonism, Head Trauma, and Surgery (44 cases) are combined to Other.

The resulting categories were then recategorized by degree of impairment. Patients in each category were divided by their degree of impairment. The neuropsychological convention regarding impairment was followed: scores greater than or equal to one standard deviation but less than two standard deviations below the age-adjusted mean indicate mild impairment; scores equal to or greater than two standard deviations but less than three standard deviations below the age-adjusted mean indicate moderate impairment; and scores equal to or greater than three standard deviations below the age-adjusted mean indicate severe impairment. Following that convention, classification by the Impairment Index is as follows: T = ≥41 unimpaired; T = 40-31 mildly impaired; T = 30-21 moderately impaired; and T = ≤20 severely impaired. Those patients whose scores on the Impairment Index were greater than 30 (greater than minus two standard deviations) were classified as normal to mildly impaired (M); those whose scores were equal to or less than 30 were classified at moderately to severely (M-S) impaired. The resulting groups are described under the heading "Recategorization By Impairment" in Figure 8.1.

The recategorization by impairment yielded 17 cells. Of those one, MIX (M-S), contained no patients; two other cells, Frontal (M-S) and Depression (M-S) contained one patient each. The Frontal (M-S) patient was included to the Other (M-S)) group and the Depression (M-S) category was deleted. Fifteen cells or groups resulted from this recategorization.

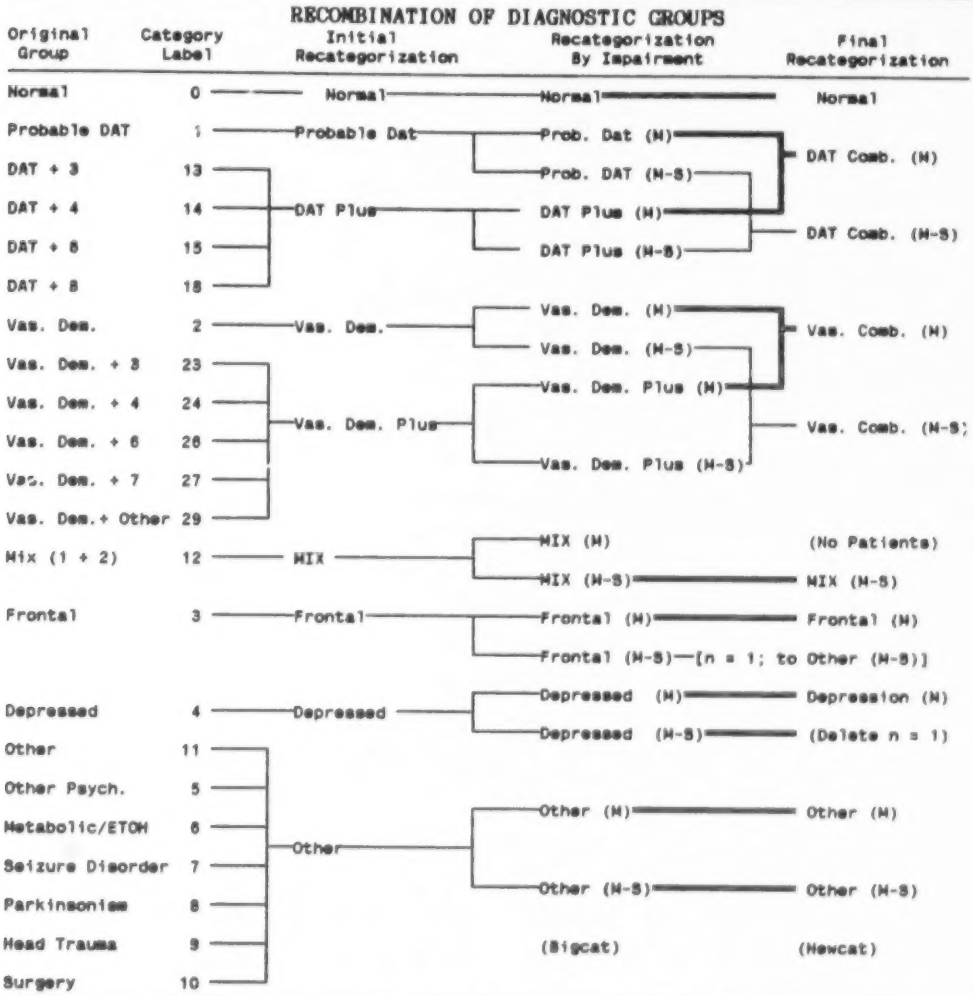
TABLE 8.4

DIAGNOSTIC CATEGORY BY SEX

Diagnostic Category	Category Label	Females	Males	Row Total	Percent
No diagnosis	-99	1	0	1	0.5
Normal	0	3	1	4	1.9
Probable DAT	1.0	22	17	39	18.6
Vascular Dementia	2.0	20	15	35	16.7
Frontal	3.0	17	10	27	12.9
Depression	4.0	8	11	19	9.0
Other Psychiatric	5.0	5	0	5	2.4
Metabolic/ETOH	6.0	0	1	1	0.5
Seizure Disorder	7.0	7	1	8	3.8
Parkinsonism	8.0	1	4	5	2.4
Head Trauma	9.0	0	2	2	1.0
Surgery	10.0	1	2	3	1.4
Other	11.0	17	4	21	10.0
Mix (1 + 2)	12.0	6	6	12	5.7
DAT + 3	13.0	2	1	3	1.4
DAT + 4	14.0	2	0	2	1.0
DAT + 6	16.0	1	2	3	1.4
DAT + 8	18.0	1	0	1	0.5
Vas. Dem. + 3	23.0	5	5	10	4.8
Vas. Dem + 4	24.0	3	1	4	1.9
Vas. Dem + 6	26.0	1	2	3	1.4
Vas. Dem + 7	27.0	1	0	1	0.5
Vas. Dem + Other	29.0	1	0	1	0.5
	Total	125	85	210	100.0

No diagnosis = no determination of probable nature of disorder; Normal = no impairment; Probable DAT = possible or probable DAT; Vascular dementia = vascular dementia/MID; Frontal = frontal deficits; Depressed = depression/'pseudodementia'; Other Psychiatric = Other Psych.= Psychiatric disorders other than depressive disorders; Metabolic/ETOH = Metabolic disorders (diabetes, hypothyroidism, medication/drug induced disorders) and alcohol abuse; Seizure Disorder = Seizure disorders; Parkinsonism = Parkinson's disease or parkinsonism; Head Trauma = closed- or open-head injury believed to be contributory to cognitive losses; Surgery = intra-cranial surgery; Other = not otherwise classifiable or infrequent diagnosis; Mix = DAT plus Vascular dementia/MID; DAT + 3 = DAT plus frontal deficits, DAT + 4 = DAT plus depression, etc.; Vas. Dem. + 3 = Vascular dementia/MID + frontal deficits, Vas. Dem. + 4 = Vascular dementia/MID plus depression,

FIGURE 8.1



Probable DAT = Probable and possible DAT; DAT + 3 = DAT plus frontal deficits, DAT + 4 = DAT plus depression, etc.; Vas. Dem. = Vascular dementia/Multi-infarct dementia (MID); Vas. Dem. + 3 = Vascular dementia/MID + frontal deficits, Vas. Dem. + 4 = Vascular dementia/MID plus depression, etc.; Mix = DAT plus Vascular dementia/MID; Frontal = Frontal deficits; Depression = depression/'pseudodementia'; Other = not otherwise classifiable or infrequent diagnosis; Other Psych.= Psychiatric disorders other than depressive disorders; Metabolic/ETOH = Metabolic disorders (diabetes, hypothyroidism, medication/drug induced disorders) and alcohol abuse; Seizure Disorder = Seizure disorders; Parkinsonism = Parkinson's disease or parkinsonism; Head Trauma = closed- or open-head injury believed to be contributory to cognitive losses; Surgery = intra-cranial surgery; (M) = Normal to Mild Impairment; (M-S) = Moderate to Severe Impairment.

The final recategorization combined DAT (possible/probable DAT) (M) with DAT Plus (M) and DAT (M-S) with DAT Plus (M-S) to create, respectively, DAT Combined (M) and DAT Combined (M-S). Vascular dementia (M) was combined with Vascular dementia Plus (M) to create Vascular Combined (Vas. Comb.) (M). The Vascular dementia (M-S) and Vascular dementia Plus (M-S) were similarly combined to create Vascular Combined (Vas. Comb.) (M-S). As there were no patients in the MIX (M) category, the final recategorization contains only MIX(M-S). Frontal becomes Frontal (M) when the single case of Frontal (M-S) is reclassified into the Other (M-S) group. The Depression category contained only 1 case in the (M-S) range and that case and range was deleted leaving only Depression (M). Other remains unchanged other than an increase in number by one in the Other (M-S) category. The final categorization yields 10 groups.

It would have been preferable to group patients by medical diagnosis, sex, three age groups (young-old, ≤65 years - 69 years; old, 70 years - 79 years; and old-old, ≥ 80 years), and three degrees of impairment (mild, moderate, and severe). One might, as well, have wish to include 3 different levels of education. Such grouping would, however, yield 90 groups, 120 groups with the inclusion of education, with, in the present study, unacceptably low numbers in each group or cell. The following compromises were made to increase cell sizes.

Few studies have reported quantitative differences in memory profiles between males and females. Validity studies of the WMS-R using both MANOVA and univariate significance tests found no significant differences between the sexes on the WMS-R Indices or on the Information and Orientation subtest with the result that no adjustment of scores by sex was deemed necessary (Wechsler, 1987). There is no normative scale against which to compare memory differences between sexes that might be found in the diagnostic groups. Sex differences would not, then, be expected to contribute to differentiating patient groups from normal controls. Removal of sex as a grouping criterion reduces the number of groups to 45 which still yields unacceptably low numbers in each cell. Sex may, however, be included as a covariate in some analyses.

Age grouping was factored into the Impairment Index by calculating the index on the basis of age-adjusted T-scores. The overall impairment index reflects impairment relative to the subject's own age group. It is argued

that it is impairment relative to ones own age group, rather than age *per se*, that is the critical variable to be examined. The number of groups was further reduced by collapsing the degrees of impairment from mild, moderate, and severe, to mild (M) and moderate-to-severe (M-S). The rationale for this adjustment arises from the focus of this investigation on *early* differential diagnosis, and similar divisions in other studies (Ober, Dronkers, Koss, Delis, & Friedland, 1986; Rosen, 1980, cited in Ober et al., 1986). From a potential treatment perspective, early diagnosis of mild and very mild cases of DAT is the primary concern, and that concern justifies focus on the differentiation of early or mild DAT patterns at the expenses of more advanced cases, that is, moderately and severely impaired cases. The direct impact of education is lost in the main analyses as a result of the compromises required to obtain acceptable cell sizes; however, education, like sex, may be a co-variate in some analyses.

STATISTICAL ANALYSES

The purpose of this investigation is to determine whether the WMS-R subtest scores, or a subset of those scores, will distinguish DAT patients from other patient groups. Linear discriminant function analysis yields a set of weights to be applied to variables so that maximum separation of two or more groups can be achieved, and appears to be the appropriate technique to achieve the separation of the subject groups by quantitative subtest performance. The quantitative performances of the groups was compared on (1) the five Indices of the WMS-R, and, in a separate analysis, on (2) the 13 subtests of the WMS-R plus two additional measures, percent retention for Logical Memory (Logical Memory II/Logical Memory I X 100) and percent retention for Visual Reproduction (Visual Reproduction II/Visual Reproduction I X 100) using discriminant function analysis. Because the WMS-R is normed only to 74 years 11 months and many of the patients exceed that age, WMS-R subtest raw scores rather than age-adjusted scores were used. Indices were calculated using the raw score weighting factors specified by the manual.

The two diagnostic categories, Recategorization by Impairment and Final Recategorization, were labelled in the analyses Big Category (Bigcat) and New Category (Newcat). The labels Bigcat and Newcat are less cumbersome and will

be used to identify the two groups in the Results chapter. Each categorization was subjected to separate discriminant function analysis by the WMS-R indices and subtests. The statistical program used is *SPSS For Windows, Release 6.0* (SPSS Inc., 1993).

A agglomerative hierarchial cluster analyses (AHCA) was performed to further examine performance patterns in the patient sample. The cluster analysis used the WMS-R subtests as dependent variables. Discriminant analysis was then used to examine the groups which emerge from the cluster analysis and the accuracy of classification of those groups.

CHAPTER 9
RESULTS

RESULTS

The focus of this investigation is the identification of score profiles that will assist in the differentiation of early DAT from other mild or early dementias or apparent dementias (pseudodementia of depression). Reporting of results will reflect that focus. The results for the moderately to severely impaired groups will be reported in tables, but those results will not be examined in detail unless some remarkable or otherwise unexpected findings emerge for those groups. The rationale for that decision is, first, the focus of the investigation, and, second, dementia, by definition, involves memory impairment and impairment of other higher cognitive functions to the extent that normal social and occupational functioning is impaired. It is unlikely that the relatively subtle differences expected with the early dementias will be discernable once a dementia is well entrenched.

The groups that are of particular interest are the Normal group, which provides a baseline against which to compare the other groups; the mild DAT groups--DAT (M), DAT Plus (M), and DAT Comb. (M); the mild vascular groups--Vas. Dem. (M), Vas. Dem. Plus (M), and Vas. Comb. (M); the Frontal group; and the Depressed group. The MIX (M) group is of interest, but there are only two cases in that group, and results obtained would be of little value.

Bigcat by WMS-R Indices: Evaluation of Hypothesis 1 Part A

The analysis yields four canonical discriminant functions. The GMI was excluded from the initial analysis because it failed to pass the tolerance test, that is, it was shown to be almost a linear combination of other dependent variables and its entry would have caused the tolerance of another variable already in the equation to drop to an unacceptable level. The results of the analysis is summarized in Tables 9.1a and 9.1b.

Table 9.1a shows that only one discriminant function, Function 1 has an eigenvalue that exceeds 1.00. That function accounts for 78.78% of the variance. A weak second function (eigenvalue .2154) accounts for another 10.28% of the variance, and two weaker functions account for the remaining

TABLE 9.1a

DISCRIMINANT ANALYSIS: BIGCAT BY WMS-R INDICES
Full categorization of Subjects

Direct method: all variables passing the tolerance test are entered.
Minimum tolerance level..... .00100

Canonical Discriminant Functions
Maximum number of functions..... 5
Minimum cumulative percent of variance... 100.00
Maximum significance of Wilks' Lambda.... 1.0000
Prior probability for each group is .06667

The following variable failed the tolerance test.

Variable	Within Groups Variance	Tolerance	Minimum Tolerance
GMI	361.919328	.0000000	.0000000

Canonical Discriminant Functions

Fcn	Eigenvalue	Pct of Variance	Cum Pct	Canonical Corr	After Fcn	Wilks' Lambda	Chi-square	df	Sig
				:	0	.249853	205.952	56	.0000
1*	1.6510	78.78	78.78	.7892 :	1	.662369	61.172	39	.0132
2*	.2154	10.28	89.06	.4210 :	2	.805059	32.201	24	.1221
3*	.1315	6.28	95.34	.3409 :	3	.910948	13.851	11	.2414
4*	.0978	4.66	100.00	.2984 :					

* Marks the 4 canonical discriminant functions remaining in the analysis.

Standardized canonical discriminant function coefficients

	Func 1	Func 2	Func 3	Func 4
VEMI	.19742	.54266	-.96227	.74798
VIMI	.39660	-.99866	-.78390	.19669
DRI	.43534	.52754	.94181	-1.11718
ACI	.35936	.04762	.90362	.49782

variance. Functions 1 and 2 are significant at $p < .0001$ and $p = .0132$. Function 1 shows strong correlations with the two summary indices, GMI and DRI, and with ViMI, and a moderate correlation with the VeMI. Function 1 is a rather general function and appears to reflect primarily level of memory impairment. The second function shows a moderate positive correlation with

VeMI (.61) and a moderate negative correlation (-.53) with ViMI as well as weak correlations with the summary indices (GMI, DRI). Function 2 may represent a weak verbal memory component; however, it may as well reflect immediate recall. Function 3 shows negative correlations with each of the true memory indices and a moderate correlation (.55) with the ACI and may represent simple attention. The ACI's strongest correlation (.63) is with Function 4 where VeMI and GMI at .20 and .10, respectively, also have weak positive correlations. Function 4 may suggest a very weak mental control function.

Classification results reveal that the WMS-R indices are little able to discriminate between the diagnostic groups. The percent of grouped cases correctly classified is 28.93%. The accuracy of classification is greater than the 7% prior probability of a given case being classified appropriately. The *Chi*-square tests yields $\chi^2 = 4.30$. At 14 degrees of freedom, p is greater than .50. The result is neither statistically nor clinically significant.

The focus of this investigation is the differentiation of early DAT, DAT (M), and DAT Plus (M) from the Normal, Vas. Dem. (M) and Vas. Dem. Plus, Depressed, and, given the large number that emerged in data collection, Frontal cases. All of those groups are in the normal to mildly impaired range.

An examination of the accuracy of classification of each of those groups reveals unacceptably low values. The accuracy of classification for the Normal group at 66.7% (2 of 3) is one of the higher values but is not reliable given the small number of cases in the group. The classification rate of Vas. Dem. (M) was 4.8% (1 of 21) and the rate for Vas. Dem. Plus (M) was 30.8% (4 of 13). The highest rate of accurate classification is in the Depressed group where 75% (12 of 16) were accurately placed. The rate of correct classification for DAT (M) was 26.7% (4 of 15) and for DAT Plus (M) the rate was 14.3 (1 of 7). Frontal cases were classified with 16.7% (4 of 24) accuracy.

The "DAT profile" must be described relative to other groups at a similar level of overall neuropsychological impairment. At this stage the "DAT profile" can only be described as low general memory (WMS-R Indices) and low verbal scores relative to the Normal group. Stepping off into

TABLE 9.1b

DISCRIMINANT ANALYSIS: BIGCAT BY WMS-R INDICES
Structure Matrix

Pooled within-groups correlations
between discriminating and canonical discriminant functions
(Variables ordered by size of correlation within function)

	Func 1	Func 2	Func 3	Func 4
GMI	.87803*	.21964	-.41408	.09678
DRI	.81803*	.27705	-.06451	-.49990
VIMI	.81036*	-.52608	-.22647	-.12357
VEMI	.64859*	.61336	-.40225	.20327
ACI	.54108	-.09198	.54908	.63030*

* denotes largest absolute correlation between each variable and any discriminant function.

Canonical discriminant functions evaluated at group means
(group centroids)

Group	Func 1	Func 2	Func 3	Func 4
Normal	.98061	1.25208	.08475	.12946
DAT (M)	-.23284	-.73314	.57324	.20857
DAT (M-S)	-2.32440	-.28405	.19316	-.19893
DAT Plus (M)	-.13107	-.08940	-.26213	.34365
DAT Plus (M-S	-1.00215	-.73047	-.09400	-.05401
Vas. Dem. (M)	-.07997	.36429	.20112	.47037
Vas. Dem. (M-)	-1.73052	.54133	.03955	-.28702
Vas. Dem. Plus (M)	.90510	-.33546	-.32362	-.26827
Vas. Dem. Plus (M-S)	-.95866	1.60166	.58705	-.29279
MIX (M)	-1.67754	-.77179	-1.09937	.23615
MIX (M-S)	-1.58599	-.06712	.05217	-.07288
Frontal	-.01105	.15236	-.43806	.12918
Depression	2.14712	.02949	.35765	-.34444
Other (M)	1.07877	-.11158	-.16493	-.00188
Other (M-S)	-1.48760	.23814	-.12251	-.68572

nonsignificance, visual memory scores may be indistinguishable from normal scores. At the same level of impairment, the mild vascular groups are not likely to be separable from those of the mild DAT groups, but there would be a tendency for verbal scores to lie between those of the normal group and the DAT group, but visual scores would lie on the other side of the DAT group.

The Frontal group general memory scores would be similar to the DAT group but verbal scores would, in general, be slightly greater. There is, of course, no legitimate clinical application for this "profile".

Newcat by WMS-R Indices: Evaluation of Hypothesis 1 Part B

Newcat reduces the number of groups from the 15 of Bigcat to 10 by combining groups. The DAT (M) and DAT Plus (M) to DAT Combined (DAT Comb. (M)) and the DAT (M-S) and DAT Plus (M-S) to DAT Combined (DAT Comb. (M-S)). Vas. Dem. and Vas. Dem. Plus were similarly combined, preserving the (M) and (M-S) separation, to Vas. Combined (Vas. Comb.). The MIX (M) and MIX (M-S) [2 cases] were combined to a single group, and the empty Frontal (M-S) group was dropped from the analysis. The single Depression (M-S) was reclassified with the Other (M-S) group.

The results of the discriminant function analysis with Newcat and the WMS-R Indices are reported in Tables 9.2a and 9.2b. As with the previous analysis, four discriminant functions were obtained and the eigenvalues were similar to those obtained in the first analysis, and GMI failed the tolerance test and was excluded. Again, Function 1 was the only function whose eigenvalue exceeded 1.00. In this analysis, Function 1 accounted for 84.07% of the variance and Function 2 accounted for 9.01%. The remaining two functions accounted for the remaining 6.91% As with the analysis of Bigcat, Functions 1 ($p < .0001$) and 2 ($p = .0244$) are significant.

Function 1 showed strong correlations with GMI (.88) and DRI (.81) and moderate correlations with ViMI (.77) and VeMI (.67) and ACI suggesting a general memory/level of impairment association. ViMI (.42) had the greatest positive correlation and VeMI has a strong negative correlation (-.58) with Function 2 implying an visual memory function. Function 3, with strongest correlations with VeMI (.45) and GMI (.39), appears to be a weak verbal memory function. Function 4 correlates moderately strongly (.72) with the ACI suggesting that that function reflects simple attention.

Classification of Newcat groups shows only an apparent improvement over classification of Bigcat. One-third (33.33%) of cases in Newcat were classified correctly as compared with 28.93% of the cases as divided by Bigcat; however, the prior probability of correct classification increased

Table 9.2a

DISCRIMINANT ANALYSIS: NEWCAT BY WMS-R INDICES
Full categorization of Subjects

Direct method: all variables passing the tolerance test are entered.
Minimum tolerance level..... .00100

Canonical Discriminant Functions
Maximum number of functions..... 5
Minimum cumulative percent of variance... 100.00
Maximum significance of Wilks' Lambda.... 1.0000

Prior probability for each group is .10000

The following variable failed the tolerance test.

Variable	Within Groups Variance	Tolerance	Minimum Tolerance
GMI	376.622773	.0000000	.0000000

Canonical Discriminant Functions

Fcn	Eigenvalue	Pct of Variance	Cum Pct	Canonical Corr	After Fcn	Wilks' Lambda	Chi-square	df	Sig
				:	0	.313234	175.281	36	.0000
1*	1.4584	84.07	84.07	.7702 :	1	.770046	39.457	24	.0244
2*	.1563	9.01	93.08	.3676 :	2	.890391	17.530	14	.2290
3*	.0812	4.68	97.77	.2741 :	3	.962696	5.741	6	.4529
4*	.0387	2.23	100.00	.1931 :					

* Marks the 4 canonical discriminant functions remaining in the analysis.

Standardized canonical discriminant function coefficients

	Func 1	Func 2	Func 3	Func 4
VEMI	.22279	-.47705	1.23334	.18324
VIMI	.32998	.87611	.75771	-.65216
DRI	.43578	-.64362	-1.45008	-.15174
ACI	.42090	.28191	-.41011	.86509

NOTE: WMS-S subtests and indices means by group for Bigcat and Newcat are presented in Appendices 2 and 3, respectively.

Table 9.2b

DISCRIMINANT ANALYSIS: NEWCAT BY WMS-R INDICES
Structure Matrix

Pooled within-groups correlations
between discriminating variables and canonical discriminant functions
(Variables ordered by size of correlation within function)

	Func 1	Func 2	Func 3	Func 4
GMI	.87653*	-.23516	.38529	-.16719
DRI	.80770*	-.38249	-.23727	-.38082
VIMI	.77084*	.42175	.09345	-.46818
VEMI	.66928*	-.58425	.45217	.07911
ACI	.58102	.37461	-.06695	.71945*

* denotes largest absolute correlation between each variable and any discriminant function.

Canonical discriminant functions evaluated at group means
(group centroids)

Group	Func 1	Func 2	Func 3	Func 4
Normal	1.03175	-1.10312	.03175	.50547
DAT Comb. (M)	-.19295	.62539	-.09945	.19562
DAT Comb. (M-S)	-2.10905	.28066	-.23393	-.07869
Vas. Comb. (M)	.30618	-.03194	.11544	.15879
Vas. Comb. (M-S)	-1.40418	-.89029	-.33656	.25009
MIX (M-S)	-1.59533	.16540	.18634	-.14585
Frontal (M)	-.01514	-.19088	.42861	-.09936
Depression	2.09608	-.03636	-.49372	-.12532
Other (M)	1.04185	.08175	.12738	-.16864
Other (M-S)	-1.48973	-.46268	-.31547	-.44309

from 7% with the 15 groups of Bigcat to 10% with Newcat, an increase of 30%. While the prior probability of correct classification increased by 30%, accuracy of classification from Bigcat to Newcat improved only 13%. The *Chi*-square test yields $\chi^2 = 2.80$; significance with df = 9 is $p > .50$. Again, the accuracy of classification is neither statistically significant nor clinically important.

The groups of particular interest are DAT Comb. (M), Normal, Vas. Comb. (M), Depressed (M), and Frontal (M). The classification rate for the Normal

group was unchanged at 66.7% (2 of 3). The third Normal case was classified as Vas. Comb. (M). The rate for DAT Comb. (M) was 36.4% (8 of 22); the other group members were classified as follows: Normal 1, Vas. Comb. (M) 1, Vas. Comb. (M-S) 2, MIX 2, Frontal (M) 2, Depressed 2, Other (M) 2, and Other (M-S) 2. Correct classification of the Vas. Comb. (M) group was 8.8% (3 of 34) with the others spread throughout the groups except Other (M-S). The majority of the Vas. Comb. (M) misclassifications were in the Normal (7) and DAT Comb. (M) (7) groups followed by Other (M) (5). Correct classification of 75% (12/16) of the Depressed group was again achieved with the other "members" of the group going to Normal 1, DAT Comb. (M) 1, and Other (M) 2. Of the Frontal (M) group, 25% (6 of 24) were correctly classified with the remainder spread through all the groups except DAT Comb. (M-S) and Vas. Comb. (M).

In the Bigcat analysis, 22.7% (5 of 22) DAT (M) and DAT Plus (M) cases were correctly classified when the two categories are considered together; in the Newcat, the DAT Comb. (M) group, the combination of the DAT and DAT Plus (M) from Bigcat, was classified with 36.4% accuracy (χ^2 = 17.03; df = 9, $p <$ .001). The accuracy of the placement of the Vas. Dem. (M) and Vas. Dem. Plus (M) groups considered together declined from 14.7% (5 of 34) to 8.8% (3 of 24) with the reclassification. The accuracy of the Frontal (M) group improved from 16.7% (4 of 24) to 25% (6 of 24). Classification accuracy for the Normal and Depressed groups was unchanged with the reclassification.

The "DAT profile" in this analysis is similar to that obtained in the Bigcat analysis; however, in this case, more confidence may be placed in the visual memory factor which emerges as Function 2 and which is significant at greater than the 95% level of confidence. While the classification of the DAT group is significant at $p < .001$, there is, again, no legitimate clinical application of this "profile".

Results of Evaluation of Hypothesis 1

Classification of clinical groups on the basis of the WMS-R Indices yields unacceptably low accuracy. With a larger number of groups (Bigcat) the classification accuracy is 28.93%. With the presumably less homogeneous, but smaller number of groups (Newcat), classification accuracy is 33.33% (by *Chi*-square test, $p > .50$). The 13% increase appears to be primarily a result of

the reduction of prior probability of correct classification. The prior probability of correct classification increases 30%, from 7% to 10%, as the number of groups is reduced from 15 to 10.

Correct classification of the group of greatest interest, early DAT [DAT (M) and DAT Plus (M)], improved from 22.7% (5 of 22) in Bigcat to 36.4% (8 of 22), and the result is significant by *Chi*-square test at $p < .001$. It appears the shift in function coefficients collected two misclassifications from the Vas. Dem. (M) group and one from the Vas. Dem. Plus (M) group. It is clear from the classification accuracies of the clinical groups in both Bigcat and Newcat that the WMS-R Indices are of little overall value in the discrimination of clinical groups; however, the DAT group classification is significant at the 99.9 level of confidence.

Hypothesis 1 asserted that *the pattern of quantitative differences among the General Memory, Attention/Concentration, Verbal Memory, Visual Memory, and Delayed Recall composite scores or indices of the WMS-R is not sufficiently sensitive to differentiate DAT from other memory disorders, but will differentiate DAT and other memory disorders from normal age-related memory change.* Discriminant function analysis of the clinical groups demonstrates that the WMS-R Indices are not, on either a statistical or clinical basis, sufficiently sensitive to differentiate DAT from other memory disorders when overall classification accuracy is considered. The first part of the hypothesis is supported. The accuracy of classification of DAT cases is, however, statistically significant, but an error rate of 64% is clinically unacceptable.

Two groups, DAT (M) and Vas. Dem. (M) were selected to test the second part of the hypothesis. Mildly impaired groups were selected to maximize the challenge of discriminating groups with memory disorders from normal age-related memory change. Of the groups of interest the DAT and Vas. Dem. groups were selected because of the clear association with memory impairment. The MIX group could have been included but there were no mildly impaired cases. Frontal and Depressed groups were not included because of the ambivalent association of those groups with true memory disorders.

Individual *t*-test between the memory indices of a normal group reflecting only age-related memory change, the WMS-R 70-74 year old

standardization sample, and the DAT (M) and Vas. Dem. (M) were calculated. Comparisons on the summary indices, GMI and DRI, were as follows: (1) GMI Normal vs. DAT (M) $t = 4.99$ (actual $p < .0005$); (2) GMI Normal vs. Vas. Dem. $t = 3.40$ (actual $p < .005$); (3) DRI Normal vs. DAT (M) $t = 4.64$ (actual $p < .0005$); (4) DRI Vas. Dem. (M) $t = 3.85$ (actual $p < .0005$). In each case critical $t = 1.67$ ($_{95}t_{60}$).

Comparison of the indices of immediate memory, VeMI and ViMI, yields the following results: (1) VeMI Normal vs. DAT (M) $t = 6.49$ (actual $p < .0005$); (2) VeMI Normal vs. Vas. Dem. (M) $t = 3.35$ (actual $p < .005$); (3) ViMI Normal vs. DAT (M) $t = 0.85$ (actual $p > .10$); (4) ViMI Normal vs. Vas. Dem. (M) $t = 1.98$ (actual $p < .05$). As above, critical $t = 1.67$ ($_{95}t_{60}$).

The Attention/Concentration Index (ACI) is not considered a memory index. ACI is a composite score of the following subtests: Mental Control, Digit Span, and Visual Memory Span. The following results suggest that the ACI serves to measure factors other than memory. That observation is supported by the observation that the ACI showed its strongest correlations with Function 4 rather than Function 1, the general memory function, in the discriminant function analysis. Comparison of the standardization sample with the DAT (M) and Vas. Dem. (M) yields the following t-values: Normal vs. DAT (M) $t = 1.22$ (actual $p > .10$); Normal vs. Vas. Dem. (M) $t = 1.68$ (actual $p < .05$). (Critical $t = 1.67$ ($_{95}t_{60}$).)

The t-test comparisons show significant differences between the mildly impaired groups and the standardization group of comparable age on the GMI and DRI. Comparison of the immediate memory indices shows a significant difference between the normal and mildly impaired DAT group on the VeMI but not on ViMI. The Vas. Dem. (M) group differed significantly from the normal group on both the indices though there was a more significant difference on the VeMI than on ViMI ($p < .005$ vs $p < .05$). ACI comparison with the normal group and the DAT group was not significant ($p > .10$), and the normal-mild vascular dementia group comparison was minimally significant at $p = .05$.

Comparison of WMS-R memory indices mean scores of the normal and mildly impaired groups with t-tests indicates that the second part of Hypothesis 1 is supported for the most part. Only one of eight t-tests failed to show a significant difference at $p \leq .05$; the ViMI failed to show a significant

difference between the normal group and the mildly impaired DAT group. The ACI comparisons were not significant for the normal and DAT group, but there was a minimally significant difference between the normal and mild vascular dementia group; however, the ACI does not appear to reflect memory processes.

The results of the *t*-test comparisons complement the discriminant analysis and support the "DAT profile" that has emerged this far: low scores on the summary memory indices GMI and DRI, and low scores on measures of verbal memory.

It is concluded that the memory indices of the WMS-R are a relatively sensitive measure for differentiating memory disorders from normal age-related memory changes, but that those indices have little value in differentiating clinical groups. The WMS-R appears to do what it was designed to do: provide a measure of memory impairment. The examination now turns to the question of whether the WMR-S can do more than provide a measure of general memory impairment.

Bigcat by WMS-R Subtests: Evaluation of Hypothesis 2

Discriminant function analysis yields 12 functions of which only Function 1 has an eigenvalue greater than 1.00 (Function 1 eigenvalue 1.8759). Functions 2 through 5 have eigenvalues between .3894 and .1943. Only Functions 1 and 2 are significant at $p \leq .05$ (Function 1 $p < .0001$; Function 2 $p = .0227$). Functions 1 - 5 account for 91.57% of the variance with Function 1 alone accounting for 57.55%. Discriminant function analysis results are presented in Tables 9.3 a, b, c, and d.

Function 1 appears, again, to be a general memory impairment function. Function 2 shows a good relationship with the verbal subtests and Function 3 with the visual subtests. Function 4 is more difficult to interpret. It shows moderate to low moderate correlations with Mental Control (.42), Visual Paired Associates I (.41), and Visual Memory Span (.35) and weak positive correlations with Visual Reproduction I (.23) and Verbal Paired Associates I (18). The function might be characterized as a mental flexibility/dealing-with-the-unfamiliar function as each of the subtests requests something of the examinee that lies outside of usual day-to-day experience. Alternatively, Function 4 may be an immediate memory function. Function 5 has moderate to

Table 9.3a

DISCRIMINANT ANALYSIS: BIGCAT BY WMS-R SUBTESTS
Full categorization of Subjects

Direct method: all variables passing the tolerance test are entered.
Minimum tolerance level..... .00100

Canonical Discriminant Functions
Maximum number of functions..... 12
Minimum cumulative percent of variance... 100.00
Maximum significance of Wilks' Lambda.... 1.0000

Prior probability for each group is .06667

Canonical Discriminant Functions

Fcn	Eigenvalue	Pct of Variance	Cum Pct	Canonical Corr	After Fcn	Wilks' Lambda	Chi-square	df	Sig
				:	0	.100884	331.452	168	.0000
1*	1.8759	57.55	57.55	.8076 :	1	.290133	178.807	143	.0227
2*	.3894	11.95	69.49	.5294 :	2	.403114	131.283	120	.2268
3*	.3016	9.25	78.75	.4814 :	3	.524712	93.189	99	.6457
4*	.2237	6.86	85.61	.4276 :	4	.642112	64.012	80	.9042
5*	.1943	5.96	91.57	.4034 :	5	.766887	38.353	63	.9940
6*	.1150	3.53	95.10	.3211 :	6	.855064	22.626	48	.9993
7*	.0544	1.67	96.77	.2272 :	7	.901611	14.966	35	.9988
8*	.0491	1.51	98.27	.2163 :	8	.945870	8.041	24	.9990
9*	.0311	.95	99.23	.1735 :	9	.975241	3.623	15	.9987
10*	.0150	.46	99.68	.1214 :	10	.989824	1.478	8	.9931
11*	.0091	.28	99.96	.0949 :	11	.998818	.171	3	.9821
12*	.0012	.04	100.00	.0344 :					

* Marks the 12 canonical discriminant functions remaining in the analysis.

strong correlations with Digit Span (.67) and Mental Control (.59) with a weaker correlation (.19) with Visual Memory Span. Function 6 is a very weak function contributing only 3.5% of the variance and virtually no significance but it is interesting for its single moderate correlation (.57) with Visual Paired Associates. Function 7 is similar to Function 6 in that it contributes little to the variance and has virtually no significance, but shows a moderate correlation (.47) with the Figural Memory subtest. These two subtests may represent unique abilities.

Table 9.3b

DISCRIMINANT ANALYSIS: BIGCAT BY WMS-R SUBTESTS
Standardized canonical discriminant function coefficients

	Func 1	Func 2	Func 3	Func 4	Func 5	Func 6
WMC	-.04519	.04971	.07740	.54301	.68512	-.30212
WFM	.02663	.16541	.31298	.00522	-.06036	-.36273
WLM1	.29480	.05912	-.24185	.21387	-.12490	.49764
WVIPA1	-.12185	-.22387	.31424	.77304	.08725	.06326
WVEPA1	.30377	.33732	-.38692	.23746	-.56376	.09787
WVR1	.48130	-.21029	-.71330	.12600	-.68081	-.42359
WDS	.31788	-.51593	-.31602	-.54373	.52127	.04831
WVMS	.03629	.36693	.49918	.25007	.01639	.52746
WLM2	-.04552	.36145	.57811	-.63609	.18414	-.66432
WVIPA2	.23569	-.24339	.04601	-.46815	-.14509	.66027
WVEPA2	-.14180	.51050	-.38025	-.12420	.47505	.18268
WVR2	.33337	-.41550	.67002	-.17541	.22334	-.04925

	Func 7	Func 8	Func 9	Func 10	Func 11	Func 12
WMC	-.57831	.41021	-.36707	-.14582	.09499	.11977
WFM	.39150	.46742	.21676	-.05642	.34271	.54921
WLM1	.64833	.71782	-.28001	-.19583	-1.28214	.27342
WVIPA1	.32398	.28103	-.16442	.48596	.11135	-.58983
WVEPA1	-.50813	.12572	.99960	.46874	-.21951	.35377
WVR1	.27962	-.14541	-.04735	-.40862	.20882	-.27562
WDS	.32640	-.23772	.44130	.28540	.00457	-.05687
WVMS	.08835	-.49803	.20634	-.56408	.07181	-.12386
WLM2	-.62051	-.19806	.20264	-.08305	.95054	-.98112
WVIPA2	-.50177	.31694	.06089	-.07345	.34876	.29227
WVEPA2	.48938	-.50603	-1.02950	-.15334	.44808	.19271
WVR2	-.22513	-.32437	-.15423	.54571	-.59390	.42575

WMC = Mental Control; WFM = Figural Memory; WLM1 = Logical Memory I; WVIPA1 = Visual Paired Associates I; WVEPA1 = Verbal Paired Associates 1; WVR1 = Visual Reproduction I; WDS = Digit Span; WVMS = Visual Memory Span; WLM2 = Logical Memory II; WVIPA2 = Visual Paired Associates II; WVEPA2 = Visual Paired Associates II; WVR2 = Visual Reproduction II: Also Tables 9.3c, 9.7b & c, & 9.10b.

Discriminant analysis of the WMS-R subtests increases the accuracy of classification with the same Bigcat group by approximately 15% over that achieved with analysis of the indices. The WMS-R Indices scores resulted in 28.93% correct classification. Analysis with the subtest scores increases the overall correct classification to 44.03%. As with the initial analysis, the prior probabilities were approximately 7%, that is, there was a 7% probability that an individual case would be correctly classified by chance

Table 9.3c

DISCRIMINANT ANALYSIS: BIGCAT BY WMS-R SUBTESTS
Structure Matrix

Pooled within-groups correlations between discriminating variables and canonical discriminant functions
(Variables ordered by size of correlation within function)

	Func 1	Func 2	Func 3	Func 4	Func 5	Func 6
WVR1	.78373*	-.21062	-.10761	.22702	-.27807	-.23933
WVR2	.65494*	-.04334	.42095	.00797	-.10897	-.17443
WLM1	.52963*	.44530	.04040	-.21943	.10708	.08646
WVEPA1	.49203	.61045*	-.21302	.18063	.00037	.08651
WVEPA2	.43391	.56952*	-.17096	-.03432	.12508	.15748
WLM2	.51098	.52402*	.18976	-.34118	.06709	-.14290
WDS	.39075	-.18872	-.23886	-.08777	.67027*	.08072
WMC	.38780	-.03541	-.14521	.41940	.58924*	-.17318
WVIPA2	.40730	-.21723	.07132	-.16430	-.16391	.57145*
WFM	.25055	.13400	.35571	.00763	-.00158	-.27835
WVIPA1	.33073	-.04348	.16508	.40862	-.03744	.28342
WVMS	.40197	.12246	.32674	.34892	.19131	.30793

	Func 7	Func 8	Func 9	Func 10	Func 11	Func 12
WVR1	.02384	-.12904	-.19943	-.23330	.16870	-.06173
WVR2	-.10076	-.30302	-.31942	.29885	-.14262	.18963
WLM1	.14818	.42682	-.12902	-.03661	-.37496	-.29961
WVEPA1	-.14979	-.03342	.20796	.47871	.04182	.04537
WVEPA2	.14090	-.13641	-.39881	.39146	.24186	.08529
WLM2	-.05840	.21874	-.08264	.12507	-.01956	-.46137
WDS	.28192	-.02859	.43981	.01022	.08511	-.10045
WMC	-.37505	.16395	-.00686	-.30923	.03237	.09957
WVIPA2	-.22242	.34449	-.22843	.02226	.42052	.06139
WFM	.47228*	.31697	.17423	-.03645	.37393	.46923
WVIPA1	.24147	.18521	-.12379	.53019*	.32283	-.34572
WVMS	.10897	-.34461	.30360	-.48638*	.06254	-.01470

* denotes largest absolute correlation between each variable and any discriminant function.

Table 9.3d

DISCRIMINANT ANALYSIS: BIGCAT BY WMS-R SUBTESTS
Canonical discriminant functions evaluated at group means
(group centroids)
Functions 1 through Function 5 only

Group	Func 1	Func 2	Func 3	Func 4	Func 5
Normal	1.36294	.97935	-1.28387	-1.64185	.55928
DAT (M)	-.18043	-1.13802	-.20311	.36550	.61047
DAT (M-S)	-2.30296	-.66974	.13728	-.14492	-.19441
DAT Plus (M)	.16754	-.33493	-1.12611	-.62807	-.53462
DAT Plus (M-S)	-1.07574	.21487	-.58526	1.00472	-.44547
Vas. Dem. (M)	-.21138	.33398	-.18340	.14423	.61484
Vas. Dem. (M-S)	-1.94783	.44181	-.01752	-.79282	.12523
Vas. Dem. Plus (M)	1.11413	-.24864	-.24057	.05211	-.55477
Vas. Dem. Plus (M-S)	-1.36080	1.41235	.88017	-.58969	.64119
MIX (M)	-1.53953	.03127	-.74494	1.03169	-1.06799
MIX (M-S)	-1.94543	.29301	1.22880	.19641	-.15720
Frontal	-.13449	.78986	-.22050	.48127	-.20318
Depression	2.22209	-.04330	.83378	-.09704	-.09278
Other (M)	1.17165	-.18862	.05919	-.08368	.03189
Other (M-S)	-1.48481	-.36004	.50200	-.71565	-.50072

alone. The *Chi*-square test yields a significance level of $p > .50$. ($\chi^2 = 9.58$, df = 14) for the Bigcat by subtest classification.

Examination of the accuracy of classification of the groups of particular interest, Normal, DAT (M), DAT Plus (M), Vas. Dem. (M), Vas. Dem. Plus (M), Frontal, and Depressed, reveals substantial improvements for most of the groups listed with the exceptions of DAT Plus (M) which was unchanged at 30.8% (4 of 13) and Depressed which remained at 75% (12 of 16) ($\chi^2 = 4.70$; $p < .05$, df = 2) accuracy. The three Normal cases were all correctly classified, an improvement of 33.3%. Correct classification of DAT (M) improved by 20% to 46.7% (to 7 of 15) ($\chi^2 = 36.29$, df = 1; $p < .001$) and classification of the DAT Plus group showed a striking 71.4% improvement to 85.7% (6 of 7) correct classification. Accuracy of classification of the Frontal group doubled from 16.7 to 33.3% (8 of 24) and yields a significant result ($p < .001$) by *Chi*-square test. The MIX (M) group--two individuals--was classified with 100% accuracy.

Despite substantial increases in accuracy of classification when the WMS-R subtests rather than indices are used, the overall accuracy is not significant at $p \leq .05$ and the accuracy within the groups of particular interest, while statistically significant for some groups, is too low to have any utility for the differentiation of clinical groups.

The "DAT Profile" continues to show weakness in the general memory function and weakness, at similar levels of impairment, of verbal memory in the two functions that are significant at $p < .05$. The Bigcat by subtest discriminant analysis yields a weak visual function which in this case appears to be significantly different than that of the normal group but not different than that of the vascular group. The weak, difficult to interpret, Function 4 tentatively identified as an immediate memory/mental flexibility function appears to be preserved relative to level of general impairment compared to the Normal group and is not substantially different than that of the vascular group. Function 5, identified as a mental control function does not distinguish between the mild groups and the normals.

Newcat by WMS-R Subtests: Evaluation of Hypothesis 2

The basis of the Newcat categorization is to increase cell sizes by combining the groups with a "pure" diagnosis with those who had a primary diagnosis of DAT or a vascular dementia and a secondary diagnosis considered to be of lesser importance. The reorganization assumes, for the purpose of the analysis, that there are underlying patterns of impairment that are characteristic of a disorder that might appear with the larger number of cases.

Nine functions emerge with discriminant function analysis of Newcat. Function 1 has an eigenvalue of 1.5951 and is the only function with an eigenvalue value greater than 1.00. Eigenvalues decline more quickly with the analysis of Newcat than with Bigcat. In the Bigcat analysis, the eigenvalues of Functions 2 through 5 ranged from .3894 to .1943. In the Newcat analysis, Functions 2 through 5 have values ranging from .3275 to .0665. In the current analysis, Function 1 accounts for 64.24% variance and Functions 1 - 5 combined account for 96.35% of the variance. Newcat discriminant function analysis results are presented in Tables 9.4 a, b, c, and d.

Table 9.4a

DISCRIMINANT ANALYSIS: NEWCAT BY WMS-R SUBTESTS
Full categorization of Subjects

Direct method: all variables passing the tolerance test are entered.
Minimum tolerance level..... .00100

Canonical Discriminant Functions
Maximum number of functions..... 9
Minimum cumulative percent of variance... 100.00
Maximum significance of Wilks' Lambda.... 1.0000

Prior probability for each group is .10000

Canonical Discriminant Functions

Fcn	Eigenvalue	Pct of Variance	Cum Pct	Canonical Corr	After Fcn	Wilks' Lambda	Chi-square	df	Sig
				:	0	.172534	258.303	108	.0000
1*	1.5951	64.24	64.24	.7840 :	1	.447748	118.118	88	.0178
2*	.3275	13.19	77.44	.4967 :	2	.594399	76.470	70	.2787
3*	.2281	9.18	86.62	.4309 :	3	.729954	46.272	54	.7634
4*	.1751	7.05	93.68	.3860 :	4	.857792	22.549	40	.9882
5*	.0665	2.68	96.35	.2497 :	5	.914855	13.081	28	.9925
6*	.0443	1.78	98.14	.2059 :	6	.955375	6.711	18	.9923
7*	.0328	1.32	99.46	.1782 :	7	.986725	1.964	10	.9966
8*	.0089	.36	99.82	.0941 :	8	.995532	.658	4	.9564
9*	.0045	.18	100.00	.0668 :					

* Marks the 9 canonical discriminant functions remaining in the analysis.

The structure matrix of within groups correlations between the WMS-R subtests and the discriminant functions is strongly similar to that obtained in the Bigcat analysis. The strong Function 1 remains a general memory function. Function 2 is clearly a verbal function with moderate correlations with Verbal Paired associates I and II (.55 and .49, respectively), a moderate correlation with Logical Memory II (.53), and a weaker correlation with Logical Memory I (.40). Function 3 is a visual Reproduction II (.39), Visual Memory Span (.32), Figural Memory (.30), Visual Paired Associates I (.29), and Visual Paired Associates II (.18). Function 4 has moderate to low moderate correlations with Visual Paired Associates I (.43), Mental Control (.31), Visual Memory Span (.30), Verbal Paired

Table 9.4b

DISCRIMINANT ANALYSIS: NEWCAT BY WMS-R SUBTESTS
Standardized canonical discriminant function coefficients

	Func 1	Func 2	Func 3	Func 4	Func 5	Func 6
WMC	.02905	.06085	-.19417	.27885	-.23902	.20796
WFM	.04457	.28633	.25274	-.05224	-.45035	.32891
WLM1	.30818	-.04246	-.03970	.51368	.23132	.94721
WVIPA1	-.09444	-.10358	.43243	.68144	.06840	.29587
WVEPA1	.21421	.31519	-.09207	.41062	-.17659	-.42582
WVR1	.36343	-.17419	-.38168	.33128	-.69953	-.02038
WDS	.37859	-.63451	-.40402	-.42255	.16683	-.32045
WVMS	.05314	.31039	.47884	.21856	.44297	-.45666
WLM2	-.01750	.49046	.15907	-.96781	-.44333	-.47502
WVIPA2	.18853	-.40085	.11850	-.35258	.38963	.28289
WVEPA2	-.08866	.33542	-.66346	-.07954	.67099	.20205
WVR2	.36847	-.27760	.55096	-.42772	.28798	-.29434

	Func 7	Func 8	Func 9
WMC	.24896	.54310	.08957
WFM	.53709	-.24659	-.02347
WLM1	-.30646	-.62354	-1.16652
WVIPA1	.38164	.32350	.30755
WVEPA1	-.06636	.56728	-.78715
WVR1	-.57804	-.43763	.47401
WDS	.49194	-.15006	-.13968
WVMS	-.03800	-.48840	.15633
WLM2	.27253	.61673	1.05811
WVIPA2	-.12423	.30105	-.00364
WVEPA2	-.07484	-.57241	.81105
WVR2	-.03521	.30996	-.57389

Associates I (.24), and Visual Reproduction (.22) and appears to be an immediate memory function. The fifth function that appears in the Newcat analysis is dissimilar to that obtained in the Bigcat analysis. Bigcat Function 5 is an attention/mental control function, but in Newcat it appears to reflect associative learning. Subtests correlated with Bigcat Function 5 are, in order of magnitude, Verbal Paired Associates II (.47), Visual Paired Associates II (.35), Visual Paired Associates I (.28), and Verbal Paired Associates I (.22). Digit Span and Visual Memory Span also correlate with this function at about .10.

The Newcat recategorization combines the mildly impaired probable DAT and probable DAT with a secondary diagnosis in DAT Comb. (M) and the vascular

Table 9.4c

DISCRIMINANT ANALYSIS: NEWCAT BY WMS-R SUBTESTS
Structure Matrix

Pooled within-groups correlations between discriminating variables and canonical discriminant functions
(Variables ordered by size of correlation within function)

	Func 1	Func 2	Func 3	Func 4	Func 5	Func 6
WVR1	.73376*	-.14337	.05626	.21839	-.33744	-.03188
WVR2	.65037*	.07847	.39470	-.14458	.04122	-.14182
WLM1	.56723*	.39620	-.09062	-.14674	.10732	.46985
WLM2	.54327*	.53370	-.01252	-.37534	.00909	.21532
WVMS	.43021*	.09357	.31696	.30267	.20778	-.41920
WMC	.42172*	-.08937	-.28089	.30736	-.20807	-.09130
WVEPA1	.50151	.54562*	-.24921	.24551	.21924	-.13354
WVEPA2	.45360	.49151*	-.30254	.02616	.46757	.14550
WVIPA1	.34242	-.02012	.28554	.43049*	.28294	.26603
WVIPA2	.39552	-.29071	.18327	-.06472	.34785	.45169*
WDS	.45340	-.32429	-.37336	-.01925	.10368	-.21578
WFM	.27336	.23415	.30222	-.05801	-.31600	.24475

	Func 7	Func 8	Func 9
WVR1	-.37011	-.09871	.34141
WVR2	-.25186	.16196	.03257
WLM1	-.03783	-.05076	-.25997
WLM2	.01010	.20985	.09379
WVMS	.14872	-.38806	.06634
WMC	.21854	.22023	-.01321
WVEPA1	.05431	.36349	-.10620
WVEPA2	-.00108	.07578	.29798
WVIPA1	.25376	.30579	.36578
WVIPA2	-.15011	.24029	.26813
WDS	.63790*	-.16884	-.07392
WFM	.53682*	-.31218	.08268

* denotes largest absolute correlation between each variable and any discriminant function.

Table 9.4d

DISCRIMINANT ANALYSIS: NEWCAT BY WMS-R SUBTESTS
Canonical discriminant functions evaluated at group means (group centroids)
Functions 1 through Function 5 only

Group	Func 1	Func 2	Func 3	Func 4	Func 5
Normal	1.38544	.76370	-1.92940	-1.53515	-.65960
DAT Comb. (M)	-.06655	-1.00967	-.32811	.18042	.10864
DAT Comb. (M-S)	-2.09810	-.43888	.16054	-.07118	-.25743
Vas. Comb. (M)	.30627	.02813	-.21756	.17280	.16035
Vas. Comb. (M-S)	-1.61333	.70274	-.14136	-.79101	.45132
MIX (M-S)	-1.78947	.49295	.78000	.21443	-.45807
Frontal	-.15507	.77507	-.19349	.51833	.02697
Depression	2.14354	.07948	.80192	-.24824	.12991
Other (M)	1.13456	-.13709	.04960	-.10577	-.32404
Other(M-S)	-1.49025	-.28799	.55864	-.71144	.24947

dementia groups--Vas. Dem. (M) and Vas Dem. Plus (M)--in Vas. Comb. (M). The DAT Comb. (M) group contains 22 cases and the Vas Comb. (M) groups contains 34 cases. The other groups of particular interest, Normal, Frontal and Depressed are unchanged. Classification accuracy with the larger DAT and Vascular groups is only marginally greater than that obtained in the Bigcat analysis--44.65% vs. 44.03%--despite the reduction in the number of groups from 15 to 10. For Newcat, the probability for the classification ratio is, by *Chi*-square test, $p > .50$ (χ^2 3.936, df = 9).

In the Bigcat analysis, 14 of 22 cases (63.6%) of mild DAT and DAT Plus patients were correctly classified into their predicted groups. The accuracy of classification of those groups declined in Newcat. Of the 22 cases in DAT Comb. (M), 13 (59.1%) were correctly classified. The accuracy of the DAT Comb. (M) group of 59.1% is significant at $p < .001$ ($\chi^2 = 58.92$; df = 9). The two mild vascular groups, Vas. Dem. (M) and Vas. Dem. Plus (M), were classified with 20.6% (7 of 34) accuracy in Bigcat, but the accuracy declined in Newcat Vas. Comb. (M) to 6 of 34 (17.6%) which by *Chi*-square is not significant ($p > .25$). Correct classification of the Normal and Depressed groups was unchanged at 100% and 75%, respectively. Classification accuracy of the Frontal group in Newcat improved to 58.3% (14 of 24) from 33.3% (8 of 24) in Bigcat. The Newcat recategorization appears to have allowed the

Frontal group to re-collect misclassifications from the DAT Plus (M), Vas. Dem. (M) and MIX (M).

The larger numbers in some groups in the Newcat recategorization yield no significant improvement in accuracy of overall classification, and a decline in the accuracy of classification of two key groups, the DAT and vascular groups. The Newcat categorization is a "two-edged sword" in that while it increases the numbers in some groups, it attenuates the "purity" of the diagnostic impression. The impact of the attenuation apparently outweighs the increased group size and leads to reduced classification accuracy. The implication of this result will be examined in the Discussion section.

The "DAT profile" is somewhat different than that obtained in the Bigcat by subtest analysis. Function 4 appears to resolve into a function that is more clearly related to immediate recall on which the DAT group is noticeable impaired relative to the Normal group, but not distinguishable from the vascular group. Performance on the associative learning function, Function 5, appears similar to that on Function 4.

A word on the "DAT profiles" in order. Interpretation has been forced for its heuristic value. In each case, only Functions 1 and 2 are significant, and the only profile of which one can speak with some confidence is impairment of general memory functions and greater impairment of verbal memory in relation to general ability when compared to the Normal group.

Results of Evaluation of Hypothesis 2

Table 9.5 summarizes the accuracy of classification for the discriminant function analyses. The table shows that classification accuracy for Bigcat improves from 28.93% to 44.03% when classification is on the basis of subtest scores rather than the composite scores of the indices. With the Newcat categorization, the improvement is from 33.33% to 44.65%. Neither the Bigcat nor Newcat classification accuracies are significant, by the *Chi*-square test, at $p < .05$, increases in accuracy of placement of 34% with Bigcat and 25% with Newcat are minimal when it is considered that variables on which placement decisions are made increase 240%--from 5 to 12. It is clear that an instrument with an overall diagnostic accuracy of 44% and an accuracy, at best, of 59% for classifying individuals with mild possible or probable DAT

Table 9.5

Classification Accuracy by Group

Group [*n*]	Recategorization By Impairment (Bigcat) Percent Correct Indices	Subtests	Group [*n*]	Final Recategorization (Newcat) Percent Correct Indices	Subtests
Normal [3]	66.7	100.0	Normal [3]	66.7	100.0
Prob. DAT (M) [15]	26.7	46.7			
Prob. DAT (M-S) [12]	58.3	50.0	DAT Comb. (M) [22]	36.4	59.1
DAT Plus (M) [7]	14.3	85.7	DAT Comb. (M-S) [14]	42.9	42.9
DAT Plus (M-S) [2]	100.0	100.0			
Vas. Dem. (M) [21]	4.8	14.3			
Vas. Dem. (M-S) [6]	33.3	66.7	Vas. Comb. (M) [34]	8.8	17.6
Vas. Dem. Plus (M) [13]	30.8	30.8	Vas. Comb. (M-S) [9]	44.4	55.6
Vas. Dem. Plus (M-S) [3]	33.3	66.7			
MIX (M) [2]	50.0	100.0			
MIX (M-S) [8]	16.7	66.7	MIX (M-S) [8]	50.0	50.0
Frontal (M) [24]	16.7	33.3			
Frontal (M-S) [0]	----	----	Frontal (M) [24]	25.0	58.4
Depression (M) [16]	75.0	75.0	Depression (M) [16]	75.0	75.0
Other (M) [22]	13.6	18.2	Other (M) [22]	27.3	22.7
Other (M-S) [7]	14.3	42.9	Other (M-S) [7]	28.6	42.9
Ungrouped Cases [20]			Ungrouped Cases [20]		
Total Correctly Classified	28.93%	44.03%		33.33%	44.65%

Probable DAT = Probable and possible DAT; DAT Plus = possible/probable DAT plus a secondary diagnosis other than vascular dementia; Vas. Dem. = Vascular dementia/Multi-infarct dementia (MID); Vas. Dem. Plus = Vascular dementia plus a secondary diagnosis other than DAT; Mix = DAT plus Vascular dementia/MID; Frontal = Frontal deficits; Depression = depression/ pseudodementia'; Other = not otherwise classifiable or infrequent diagnoses; DAT Comb. = Probable DAT and DAT Plus combined; Vas. Dem. Comb. = Vas. Dem. and Vas. Dem. Plus combined; (M) = Normal to Mild Impairment; (M-S) = Moderate to Severe Impairment.

has very limited utility in the separation of clinical groups.

The classification results raise a conundrum. The *Chi*-square test (Goodness of Fit) demonstrates that the rates of classification obtained, given the numbers and prior probabilities, were highly significant ($p < .001$) for the mild DAT and Frontal groups and significant ($p < .05$) for the Depressed group but not significant for the vascular group or for overall

classification in either Bigcat and Newcat. Is Hypothesis 2 supported because the DAT classification accuracy has respectable statistical significance even though the overall classification is not significant?

Hypothesis 2 states that *the pattern of quantitative differences among the subtest scores of the WMS-R, or a subset of those scores, is sufficiently sensitive to differentiate DAT from other memory disorders and from normal age-related memory changes.* The conundrum described in the previous paragraph suggests the hypothesis was inadequately formulated. As the focus of this investigation is the clinical utility of the WMS-R, Hypothesis should have read "The pattern of quantitative differences among the subtest scores of the WMS-R, or a subset of those scores, is sufficiently sensitive to differentiate DAT from other memory disorders and from normal age-related memory changes *at not less than 85% accuracy.*" That rate would rival the accuracy of neuropathological classification. With a misclassification rate for the DAT cases of 41% in this study, it cannot be argued that the subtests of the WMS-R are sufficiently sensitive to differentiate DAT from other memory disorders and from normal age-related memory changes on a clinical basis, despite statistical significance for the classification of the possible/probable DAT cases. Hence, while Hypothesis 2 is statistically supported, in the narrowest sense, the use of a WMS-R subtest profile alone for clinical decision making is not supported.

The WMS-R subtests were, however, able to separate the mild DAT cases with about 60% accuracy which in this circumstance is significant at $p < .001$ as compared with approximately 18% ($p > .10$) for cases of mild vascular dementia. Poor selection of the vascular cases is not unexpected as individuals in that group will have lesions in many different brain areas and performance on the WMS-R subtests would be expected to vary depending on the location and volume of the lesion. There is little reason to expect a uniform profile for the vascular group.

The Depressed group, another group with which early DAT may be confused, was selected with 75% accuracy in this study regardless of whether the WMS-R index or subtest variables are used in group classification. The literature reviewed in Chapter 4 Review of the Literature--Issues in Differential Diagnosis suggest that there is a relatively consistent pattern of performance

of depressed individuals on a variety of memory measures. In this study, however, the Depressed group appears to be well selected primarily on the basis of high scores especially on visual measures. The mean subtest scores of the Depressed group were greater than those of Normal group on every visual measure and on the GMI. This result would not be anticipated on the basis of the review of literature, and likely represents a selection bias resulting from the physicians' decision to refer patients with a certain clinical presentation and not others.

The Frontal group is selected with almost equal accuracy as the early DAT group. This is a somewhat surprising result as the diagnosis or impression of frontal disorders is made primarily on measures other than memory performance. Examination of the canonical discriminant functions evaluated at the group centroids (Table 9.4d) indicates that the Frontal group separates from the DAT group on the basis of the verbal memory function with small input from the weak mental control function and from the Normal group on the general memory, visual memory and attention/concentration functions.

With each of the groups in the Newcat analysis the prior probability of selection is 10%. The mild groups for which there is some reason to believe, on the basis of the literature or clinical experience, a relatively distinctive profile of performance on different measures of memory may exist are selected at approximately six times greater than chance. The results obtained raise a key question, "Do the mediocre classification rates arise because there are no diagnostic profiles or because the WMS-R subtests not sufficiently sensitive?" This question will be addressed in the Discussion section.

ADDITIONAL ANALYSES

Comparison of WMS-R Scores of Normal, Mild DAT and Mild Vascular Cases

The selected WMS-R scores of the Normal, mild DAT and mild Vascular cases were compared with *t*-tests. Because the Normal group in the sample consistes of only four cases, one of which was excluded from most analyses because of missing data, the 70-74 year old group from the WMS-R standardization sample was used as the Normal group in *t*-tests. Despite the small sample size, it is interesting to note that the means of the three

normals in the study differed significantly ($p < .05$) from the 70-74 years-olds in the standardization sample on only one subtest, Visual Memory Span. The comparisons are summarized in Table 9.6. Those scores on which the mild DAT group differed from the Normal group by ≥ 1 standard deviation were selected for this brief comparison.

The results of the *t*-test comparisons support the discriminant function analysis. The mild DAT group differs from the Normal group on general memory--the WMS-R Indices--represented in Function 1 in all analyses and on verbal memory/verbal ability--Logical Memory I, Verbal Paired Associates, and Logical Memory II--represented in Function 2. A weak visual function emerged in the discriminant analyses with the subtest as Function 3. The weakness of the

Table 9.6

Comparison of WMS-R Scores: Mild DAT and Mild Vascular Cases with WMS-R 70-74 year old Standardization Sample by *t*-Test

WMS-R Subtest/Index	Normal Mean (SD)	DAT Mean (SD)	Vascular Mean (SD)	Significance of Difference: $p =$ Normal-DAT	Normal-Vas.	DAT-Vas.
Logical Memory I	20.9 (7.3)	9.8 (3.2)	14.5 (4.7)	.0005	.005	.025
Verbal Paired Assoc. I	16.8 (4.0)	9.8 (4.2)	14.2 (4.7)	.0005	.01	.005
Logical Memory II	14.7 (9.2)	4.0 (3.1)	8.6 (7.5)	.0005	.005	.025
Verbal Paired Assoc. II	4.0 (1.9)	4.1 (1.9)	5.6 (1.7)	.0005	.005	.05
Visual Reproduction II	16.5 (8.3)	9.8 (11.6)	8.7 (6.3)	.01	.0005	.25
Verbal Memory Index	58.7 (17.1)	29.3 (8.6)	43.2 (19.3)	.0005	.005	.01
General Memory Index	97.2 (23.5)	65.5 (15.0)	76.6 (22.8)	.0005	.005	.05
Delayed Recall Index	52.6 (17.4)	29.0 (17.7)	36.0 (14.6)	.0005	.0005	.05

visual function, or perhaps more precisely, the weakness of the WMS-R's ability to assess visual abilities, is shown in at least two ways in the *t*-test comparisons. First, the mild DAT group mean on only one visual memory subtest, Visual Reproduction II, lies more than one standard deviation below the mean of the Normal sample. Second, the difference in means for Visual

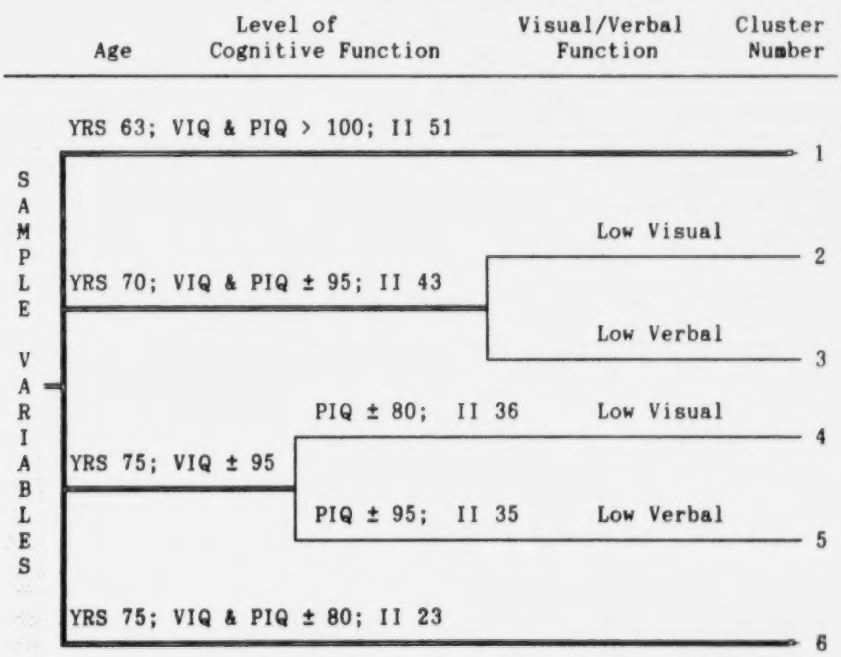
Paired Associates I, Visual Reproduction I, and the Visual Memory Index between the Normal and Mild DAT group is not significant at $p < .05$. There is a significant difference between the Normal group and the mild vascular group means on Visual Reproduction I ($p < .025$) and the Visual Memory Index ($p < .05$), but not on Visual Paired Associates I ($p > .25$).

Cluster Analysis

On the basis of the agglomerative schedule and resulting Euclidian distances, a cluster analysis breaking the total groups into six clusters was selected for the initial analysis. The results of that analysis are illustrated in Figure 9.1

Figure 9.1

Schematic Representation of Cluster Analysis



YRS = rounded mean age of group; VIQ = Verbal IQ; PIQ = Performance IQ; II = Impairment Index (rounded); Low Visual = poorer performance on visual measures; Low Verbal = poorer performance on verbal measures.

Classification analysis on the basis of six clusters essentially recapitulates the results of the discriminant function analyses of Bigcat and Newcat. The initial clustering appears to segregate by level of cognitive functioning and yields four groups, a normal or better group (Cluster 1), a moderately to severely impaired group (Cluster 6), a low normal group (Clusters 2 and 3), and a mildly impaired group (Clusters 4 and 5). At the second step, the low normal (Clusters 2 and 3) and the mildly impaired groups (Clusters 4 and 5) are divided on the basis of verbal and visual memory/ability to form the separate Clusters 2, 3, 4, and 5.

Step 1 appears to correspond to Function 1, general memory/level of impairment function found at significant levels ($p < .0001$) in each of the four discriminant function analyses. Step 2 corresponds to Function 2 which is a verbal function and significant at $p = .02$ (±) in all the discriminant analyses. Analysis of the cluster groupings appears to suggest a true visual function as Function 3 which corresponds to Function 3 in Bigcat and Newcat. With Cluster analysis, a fourth significant function is identified that appears to reflect associative learning. An associative learning function emerges in the Newcat discriminant function analysis as Function 5 but its significance is $p > .99$; whereas, Function 4 in the Cluster Groups discriminant function analysis is significant at $p = .0002$. Discriminant analysis of the Cluster groups is presented in Tables 9.7 a, b, c, and d.

Classification of the Cluster Groups after discriminant analysis yields impressive results. The 179 cases remaining in the analysis after the exclusion of cases with missing data are classified with an overall accuracy of 93.3% (prior probability 16.7%). Groups 1, 2, and 6 are classified with 100% accuracy. Groups 3, 4, and 5 are classified, respectively, at 87.9%, 89.2%, and 90.2% accuracy. In this case the accuracy of classification levels are clinically acceptable, but the information gained is little more than can be obtained by perusing the WMS-R Indices.

Commentary on Additional Analyses

The additional analyses support the result of the discriminant analyses. The pattern that emerges repeatedly is of a general memory function reflecting level of impairment, a verbal function, and a weak visual function. With the

Table 9.7a

DISCRIMINANT ANALYSIS: GROUPS DEFINED BY CLUSTER ANALYSIS
On groups defined by Cluster=6 Ward Method

Direct method: all variables passing the tolerance test are entered.
Minimum tolerance level..... .00100

Canonical Discriminant Functions
Maximum number of functions..... 5
Minimum cumulative percent of variance... 100.00
Maximum significance of Wilks' Lambda.... 1.0000
Prior probability for each group is .16667

Canonical Discriminant Functions

Fcn	Eigenvalue	Pct of Variance	Cum Pct	Canonical Corr	After Fcn	Wilks' Lambda	Chi-square	df	Sig
				:	0	.018623	673.186	60	.0000
1*	8.1957	75.99	75.99	.9441 :	1	.171253	298.220	44	.0000
2*	1.5561	14.43	90.41	.7802 :	2	.437732	139.619	30	.0000
3*	.7264	6.73	97.15	.6487 :	3	.755685	47.342	18	.0002
4*	.2444	2.27	99.41	.4431 :	4	.940343	10.395	8	.2384
5*	.0634	.59	100.00	.2442 :					

* Marks the 5 canonical discriminant functions remaining in the analysis.

Table 9.7b

DISCRIMINANT ANALYSIS: GROUPS DEFINED BY CLUSTER ANALYSIS
Standardized canonical discriminant function coefficients

	Func 1	Func 2	Func 3	Func 4	Func 5
WMC	.01914	-.06505	.29105	.07165	.25107
WFM	-.04664	-.18916	-.09159	.07323	.31951
WLM1	.08076	.44719	-.16122	.43759	-.17387
WVIPA1	.34777	-.14238	-.22081	.31444	.03028
WVEPA1	.10814	.31253	.29536	.19633	-1.08983
WVR1	.31589	-.23137	.83627	.03225	.20744
WDS	.03370	-.08454	.01649	-.64348	-.13911
WVMS	-.10493	.07188	-.02412	-.05759	.04645
WLM2	.36391	.51239	-.02007	-.63999	.34569
WVIPA2	-.06622	.13949	.17622	-.25881	-.52603
WVEPA2	.06650	-.12377	.00382	.63895	.95168
WVR2	.69874	-.43727	-.60291	-.14468	-.19989

Table 9.7c

DISCRIMINANT ANALYSIS: GROUPS DEFINED BY CLUSTER ANALYSIS
Structure Matrix

Pooled within-groups correlations between discriminating variables and canonical discriminant functions
(Variables ordered by size of correlation within function)

	Func 1	Func 2	Func 3	Func 4	Func 5
WVR2	.74377*	-.40330	-.31717	-.11573	-.10662
WLM2	.49122	.74378*	-.06196	-.24375	.29709
WLM1	.38776	.67352*	.03005	.00455	.11055
WVR1	.50534	-.26611	.70391*	-.12730	.11411
WMC	.13619	-.00335	.45440*	-.12739	.07116
WVEPA2	.31938	.19621	.06573	.61981*	.19895
WVEPA1	.31210	.29085	.19298	.48975*	-.39106
WDS	.10481	.05564	.26982	-.35987*	-.03719
WVIPA1	.24429	-.03951	.02767	.33030*	-.15193
WVMS	.15477	-.03883	.18311	-.19075*	-.00039
WFM	.13964	-.08201	-.01337	.07730	.30794*
WVIPA2	.19232	-.00495	.22174	.02226	-.26461*

* denotes largest absolute correlation between each variable and any discriminant function.

Table 9.7d

DISCRIMINANT ANALYSIS: GROUPS DEFINED BY CLUSTER ANALYSIS
Canonical discriminant functions evaluated at group means (group centroids)

Group	Func 1	Func 2	Func 3	Func 4	Func 5
1	5.76300	-.14240	-.49724	-.45512	-.58059
2	1.87369	1.80965	.51472	-.44933	.28442
3	2.56487	-1.61744	-.30450	.35899	.26857
4	-1.16684	1.21942	-.27379	.73877	-.12612
5	-2.20820	-.86641	1.17235	-.12966	-.11670
6	-3.82139	-.27352	-1.47316	-.58366	.04370

six groups cluster analysis, significance at greater than the 95% level of confidence was obtained for the first four of five factors as compared with significance at that level in only the first two factors in the discriminant analysis. The task set for the cluster analysis--group 210 cases into six

homogeneous groups--was, however, somewhat simpler than that set for the discriminant analyses which demanded sorting into 15 and 10 groups on the basis of differences. A 10 or 15 group cluster analysis could have been undertaken, but analysis must stop somewhere and additional cluster analysis would have questionable justification on the basis of the Euclidian distances obtained.

RESULTS--CLOSING COMMENTS

A "DAT profile" of low scores on the summary indices (GMI and DRI) and low scores on the immediate recall verbal index (VeMI), relative to level of impairment, emerges in each discriminant analyses. The accuracy of detection of the profile increases from a maximum of 36.4% with the indices (Newcat by indices) to 59.1% with the subtests (Newcat by subtests). The rate of correct classification in each case is significant ($p < .001$) while overall classification for all groups in each case is not significant ($p > .50$). However, while the selection of DAT cases is statistically significant, a "profile" with an error rate of 40%, has little clinical utility.

Specificity

While overall accuracy is low, and correct classification of DAT cases (sensitivity) is, at best, borderline, specificity is high. Specificity, the correct identification of non-DAT (M) cases, ranges from a low 87.90% in the Bigcat by indices analysis to a high of 94.51%, significant at $p < .001$ ($\chi^2 = 10.92$; ${}_{99.9}\chi_1 = 10.8$), in Bigcat by subtests. Even when the groups not likely to be misclassified as mild DAT, i.e., the moderately to severely impaired cases, are removed, specificity remains high at 88.24% ($\chi^2 = 16.8$) in the analysis yielding the greatest sensitivity for DAT, Newcat by subtests.

Clinically, it is clearly important to be able to say with 90% accuracy that an individual does not suffer DAT. However, even 90% correct rejection leaves one group that might be confused with early DAT, mild vascular dementia, poorly defined. Nineteen percent of cases of "pure" mild vascular dementia were misclassified in the Bigcat analysis and 23.5% of mild Vas. Comb. were misclassified in the Newcat analysis. (It is speculated that the

mechanism for the misclassification is cerebral vascular lesions in the posterior association cortices, especially on the left, that mimic DAT.)

The strong specificity is an important finding that deserves further investigation and amplification in future papers, but it adds little to understanding the problem set here which is how the "DAT" profile looks in the WMS-R.

CHAPTER 10

DISCUSSION

> The *Wechsler Memory Scale--Revised* (WMS-R) is an individually administered, clinical instrument for appraising major dimensions of memory functions in adolescents and adults. The scale is intended as a *diagnostic* [italics added] and screening device for use as part of a general neuropsychological examination, or any other *clinical examination* [italics added] requiring the assessment of memory functions. The functions assessed include memory for verbal and figural stimuli, meaningful and abstract material, and delayed as well as immediate recall. (Wechsler, 1987, p. 1)

and

> The WMS-R is intended to assist in the clinical evaluation of a variety of memory functions, *for such purposes as evaluating the pattern and localization of organic brain damage, providing information helpful in the diagnosis of brain dysfunction* [italics added], exploring changes in patient status following therapy, and providing information relevant to the training and rehabilitation of patients. (Wechsler, 1987, pp. 6-7)

These statements from the *Wechsler Memory Scale--Revised Manual* (1987) identify the WMS-R as a clinical instrument with the intended purpose of identifying patterns of memory loss and the relation of memory loss to organic brain damage and the localization of that brain damage. The studies by Chelune and Bornstein (1988) and Loring et al. (1989) cited in the review of literature examining the WMS-R do not support the claim that the WMS-R is of great value in localizing brain lesions. However, in making those claims the WMS-R is opened to investigations of the sort undertaken in this research.

The results obtained here show the WMS-R to be of limited value in identifying patterns of impairment in different clinical groups, whether the performance of those groups was evaluated on the indices or the subtests. Neither the indices nor the subtests were able to sort 10 patient groups with

an overall accuracy of greater than 44.65% which represents a confidence level of less that 50%.

While there may be a number of reasons why the WMS-R was unable to classify patients with an accuracy acceptable for clinical practice, two possibilities are immediately apparent: (1) there is no real difference in the pattern of impairment of memory functions or modalities between the groups, and (2) there are patterns, but the WMS-R indices and subtests are not sensitive enough to differentiate the real differences in patterns of memory impairment in the clinical groups. A third possibility logically follows: (3) the WMS-R does not discriminate well because the differences in the patterns of impairment are subtle and the WMS-R is sensitive to large differences in memory performance but not subtle ones.

There is a significant body of literature, some of which is reviewed in the chapter on differential diagnosis in this work, that suggests there are detectable differences in patterns of memory impairment between clinical groups. That literature suggests that the differences are most discernible at early stages of impairment. For groups with true progressive dementias there is a point when dementia is dementia, and differentiation by etiology is possible only on the basis of history. For that reason, close examination of the clinical groups in this investigation has focused on the mildly impaired groups rather than the moderately to severely impaired groups.

In this investigation, the groups identified with the greatest accuracy in the final recategorization were, in order of accuracy of classification, Normal, Depressed, mild DAT, Frontal, and moderately to severely impaired Vascular Combined. Accurate classification of the small normal group is not unexpected. What is perhaps unusual is the inclusion of normals in the sample. It is likely that these individuals were referred for assessment on the basis of self-perceived memory changes. Relatively high accuracy of classification of the Depressed group was anticipated but not of the Frontal group.

It was expected that the Depressed group would show deficits in attention and concentration and, as a result somewhat lower than normal scores on the immediate recall with relatively better delayed recall scores and normal percent retention. It appears, however, that the Depressed group in this case is classified on the basis of exceptional performance. The

performance of the Depressed group exceeded the performance of the Normal group on each of the indices save the Verbal Memory Index, and a review of the group means for canonical discriminant functions in the Newcat by subtest analysis shows that the Depressed group exceeded the Normal group on all functions except Function 2, the verbal function.

There is no compelling support in the literature for a true verbal memory deficit in depressed populations. There is, however, ample support for the suppression of effortful processing in that population. The verbal subtests and Logical Memory, in particular, demand the greatest effortful processing. Logical Memory I demands the longest period of sustained attention, and recall and recitation of the stories for both immediate and delayed recall demands sustained verbal production. It seems most probable that the low scores on the verbal index result from impairment of effortful processing rather than a true verbal memory deficit.

Classification of the Frontal group at 58.3% accuracy ($p < .001$) was not anticipated. As indicated in the Results section, determination of frontal deficits is usually made on measures other than the WMS-R. Accurate selection of the Frontal group appears to be possible on the basis of Newcat by subtests discriminate analysis Functions 1 and 2. On Function 1 the discriminant function coefficient of the Frontal group evaluated at group centroids, -.15507, approaches that of the mild DAT group, -.06655, more closely than any other group, while on Function 2 the Frontal Group's discriminant function coefficient, .77507, is minimally different from that of the Normal group, .76370. Function 1 reflects general memory impairment and Function 2 reflects verbal memory. There are no other groups which show this relationship between the two functions.

The Vascular Dementia moderate to severe group (Vas. Comb. (M-S) with nine members was selected with 55.6% accuracy. That selection was, again, primarily on the basis of the first two functions. Only two groups, DAT Comb. (M-S) and MIX (M-S) at -2.09810 and -1.79847, respectively, had group centroids lower than the Vas. Comb. (M-S) group at -1.61333. However, on Function 2 (verbal), the Vas. Comb. (M-S) group at .70274 approached the Normal and Frontal groups. The level of classification accuracy for this group appears suspect and the *Chi*-square test indicates that there is good

reason for caution. By *Chi*-square test the confidence level of this result is less than 90% ($\chi^2 = 2.245$; $_{90}\chi^2_1 = 2.71$). As observed in the Results section, there is no reason to expect a consistent profile for patients with an early vascular dementia. The nature of impairment is expected to vary with the location and the volume of the cerebral vascular lesions. That expectation is confirmed in the Newcat by subtests discriminant analysis where the classification accuracy of the mild vascular cases is 17.6% ($p > .10$).

The "DAT Profile"

The greatest accuracy of classification for the group of greatest interest, mild DAT, was in the Newcat by subtests discriminant function analysis where it reached 59.1%. As noted in the Results section, that value is significant at $p < .001$ by the *Chi*-square test. Primary selection is on the basis of Functions 1 and 2. On Function 1, the group centroid for the mild DAT group is -.06655, compared with 1.38544 for the Normal group, 2.14354 for the Depressed group, .30627 for the mild vascular group, and -.15507 for the Frontal group, but on Function 2 the comparisons are mild DAT -1.00967, Normal .76370, Depressed group .07948, mild vascular group .02813, and Frontal .77507. These comparisons show that, relative to impairment of general memory, verbal memory is more impaired in the DAT group than in any other group.

Some studies (Capitani et al., 1990; Chui et al., 1985) have suggested that verbal memory deficits are prominent in early DAT, while others (Martin et. al., 1986; Haxby, 1990) have tended to find more or less equal numbers of DAT patients with global, left-sided (verbal), and right-sided deficits (nonverbal). The results of this investigation appear to support Capitani et al. *if it is assumed that the WMS-R measures verbal and nonverbal deficits/abilities with equal facility.*

Throughout the analyses with the subtests, a visual or nonverbal function has tended to emerge with low eigenvalues, a 9% contribution to explaining variance, and significance in the .2 to .3 range. In the opening paragraphs of this section, the questions were raised whether the WMS-R's failure to adequately differentiate the groups in the analyses was a result of the absence of pattern of real memory difference between the clinical groups

or the insensitivity of the instrument. In the Bigcat by subtest discriminant analysis, the visual function (Function 3) group centroid for the Normal group is -1.28387, -.20311 for the "pure" mild DAT group, the DAT groups without a secondary diagnosis, -.18340 for the "pure" vascular group, -.22050 for the Frontal group, and .83379 for the Depressed group. There is no clear separation between the mild DAT group and the other mildly impaired groups. Comparison of means on the Visual Memory Index for a normal group--the WMS-R 70-74 year old standardization sample , mild DAT, and mild Vascular groups is instructive. The means of the standardization sample are substituted because of the small size of the sample Normal group and the failure of the Visual Memory Span of that group to reach the 95% level of confidence. The standardization group is identified as 'WMS-R Normal' group to avoid confusion with the sample group. The ViMI (raw score) means and standard deviations are as follows: WMS-R Normal 38.50 (10.30), mild DAT 36.19 (10.09), and mild vascular 33.46 (7.98). The difference between the ViMI means of the WMS-R Normal group and the DAT group is not significant, by *t*-test comparison, at $p < .05$. The difference between the WMS-R Normal and Vascular group is significant at the 95% level of confidence. Comparison of the visual subtests reveals that the mild DAT group mean is impaired--more than one standard deviation below the mean of the WMS-R Normal group--on only one subtest: Visual Reproduction II, a delayed recall test. The mild DAT means for Visual Reproduction I and Visual Paired Associates I and the means of the WMS-R Normal group are not different at $p < .05$. There is a significant difference between the Vascular group and the WMS-R Normal group on Visual Reproduction I but not Visual Paired Associates I. Figural Memory is not included in analysis of visual subtests as it appears to load more substantially on an attention/concentration factor (Loring, 1989) than visual memory.

A number of difficulties with the visual subtests were noted in the review of the WMS-R in Chapter 6. The first is the failure of the Figural memory subtests to load more substantially on a visual factor than an attention factor and that there is no delayed recall of that subtest. Second, it is asserted that Visual Paired Associates contains a significant verbal component because of a tendency of persons to employ verbal labelling in that subtest. Third, this investigator has identified difficulties with scoring of

the Visual Reproduction subtests that indicates that the current scoring protocol fails to account for differences in the recall of global and local elements which appear to be important in localization of left- and right-hemisphere deficits (Delis et al, 1992). That difficulty is reflected in the inability of the WMS-R Visual and Verbal subtest to differentiate epilepsy patients whose seizures originated in the left temporal lobe from those which originated in the right temporal lobe, and the failure of the indices to correctly identify patients who had undergone either a unilateral left or right temporal lobe resection (Loring et al. 1988). In the latter case, the indices were not only unable to differentiate, but in some cases suggested resection of the lobe that had not been resected. Fourth, Chelune and Bornstein (1988) found for patients with unilateral lesions a right-left difference for the Verbal Memory Index only. Finally, the Visual Memory index has the lowest reliability and greatest standard of measurement of all the indices.

It is clear that there are significant weaknesses in the visual subtests and the Visual Memory Index. Those weaknesses suggest that the inability of the WMS-R Indices and subtests to differentiate clinical groups accurately arises, at least in part, in the insensitivity and low reliability of the visual subtests as differences between DAT patients and normal individuals are found in a number of studies (Delis et al., 1992; Martin et al., 1986, Haxby, 1990; Coyne, Liss, & Geckler, 1990; Becker et al. 1987) using other instruments.

Given the weakness of the WMS-R visual subtests and the VeMI, it cannot be argued that the "DAT profile" consists only of greater verbal memory dysfunction relative to general memory function/level of impairment; it is probable that other patterns of memory difference between mild DAT patients and normals are not detected with the WMS-R. The next section explores some of the additional elements in the "DAT profile".

Enhancing the WMS-R's ability to find "DAT Profiles"

Studies examining the differential diagnosis of DAT have found that performance in the following areas appears to differentiate DAT patients from other groups: learning effect; primacy and recency; interference and intrusions; ability to benefit from cuing; recognition and generation of false

positives; immediate recall-delayed recall comparisons. The "DAT profile" would be characterized, relative to other groups at a similar level of impairment, (1) by no or minimal learning effect; (2) recency is greater than primacy in recall; (3) a greater number of non-list or non-story items as intrusions, and transpositions on verbal paired associate learning; (4) no or minimal ability to benefit from cuing; (5) impaired recognition and a greater proportion of false positives; and (6) delayed recall shows greater impairment than immediate recall.

The absence of a list learning task in the WMS-R is a major weakness, as is the absence of recognition measures. The WMS-R formally measures only one item from the list in the previous paragraph, i.e., delayed recall in relation to immediate recall; however, it appears that a number of the elements listed are available in the WMS-R but are not measured. Intrusions of non-story items, and transpositions between Story 1 and Story 2 can be measured in Logical Memory I and II. Transpositions and intrusions in Verbal and Visual Paired Associates I & II can be counted. A learning effect can be recorded for Visual and Verbal Paired Associates I. The ability to benefit from cuing could be assessed by asking probe questions following the administration of Logical Memory II and Visual Reproduction II. Inclusion of these measures in the scoring should enhance the ability of the WMS-R to differentiate DAT cases from other memory disorders. In conclusion, it is noted that all of the measures described here which best discriminate DAT from other disorders are verbal measures.

A number of researchers have found recognition memory to be highly sensitive in the differentiation of DAT patients from both normal and depressed individuals as well as from other groups (La Rue, 1982; Poitrenaud, Moy, Girousse, Wolmark, & Piette, 1989; Morris, Wheatley, & Britton, 1983; Davis & Mumford, 1984; Wilson, Bacon, Kramer, Fox and Kaszniak, 1983). The absence of recognition measures represents a significant weakness in the WMS-R. In response to that criticism this investigator has, in a separate study, developed a set of recognition subtests for Logical Memory, Visual Paired Associates, Verbal Paired Associates, and Visual Reproduction categories of the WMS-R. While the numbers are still low (n = 21) the Recognition Extension has yielded promising results. DAT patients have shown little

difference on the recognition measures when their recognition scores are compared to the WMS-R indices, while two individuals with well documented affective disorders have produced WMS-R Index scores that would suggest significant organic impairment and that are well below (≥ 1 SD) the mean of the clinical group on the same measures, but recognition scores that exceeded those of the clinical group by a full standard deviation or more and suggest normal performance. Other groups, primarily frontal disorders and vascular dementias with demonstrated lesions, have produced a different pattern of relationships between the WMS-R indices and the recognition subtests that are not carefully analyzed at this time.

An "Alzheimer's Profile" Among The Subtests of the Wechsler Memory Scale--Revised?

The answer to the question posed is, unfortunately, equivocal. A clear relationship between level of impairment of a general memory function and a verbal memory function emerges for the group of DAT patients in this study: relative to general memory, verbal memory is more impaired. That result is found at varying degrees of significance in each analysis whether the analysis is of indices or subtests, but it emerges more strongly with the subtest analysis. The two functions on which it emerges have acceptable significance and account for not less than 69.5% of the variance when the subtests are used in the analysis. The best rate of classification accuracy achieved for a DAT group is 59.1% which is significant at $p < .001$. It is interesting that that rate of accuracy is achieved with the DAT Comb. (M) group, a group that includes not only "pure" DAT patients, but those with a secondary diagnosis. That result appears to suggest that there is a "DAT profile" that "breaks through" in spite of the secondary diagnosis. However, a classification accuracy of 59.1% has limited value in that slightly more than 40% of the patients will be misclassified, and that is a misclassification rate that is unacceptable in clinical practice. It appears that the classification accuracy of the WMS-R might be improved if the information available within the WMS-R, i.e., learning curve, intrusions and transpositions, and ability to benefit from cuing or probe questions, was utilized.

The assessment of nonverbal or visual memory with the WMS-R is problematic. Other research cited suggests that there are differences between visual memory functions in DAT patients and other clinical groups. That finding does not appear at significant levels in this study, though it does appear weakly. The literature reviewed indicates that there are substantial difficulties with the visual or nonverbal subtests of the WMS-R. The evidence of differences in visual memory between DAT groups and other clinical groups argues against the conclusion that there are no significant differences in visual memory that will assist in the differentiation of DAT. The stronger hypothesis is that there are differences in visual memory between DAT and other groups, but the WMS-R visual subtests as currently constituted and scored are not sufficiently sensitive to detect those differences.

This investigation must conclude that the answer to the question "Is here an Alzheimer's profile among the subtests of the WMS-R?" is equivocal. While the WMS-R detects the "DAT profile" at statistically significant levels, the investigator's failure to specify the criterion for clinical significance or clinical utility leaves the question unanswerable.

CLINICAL IMPLICATIONS

The WMS-R is designed to be part of a larger neuropsychological battery, and no competent clinician would attempt to form a diagnostic impression on the results of a single instrument; however, the pattern of memory impairment, as opposed to simple level of memory impairment, is a relevant to forming a diagnostic impression. The results of this investigation suggest that a clinician would be well advised to consider the relationship of verbal memory impairment to overall impairment. If verbal memory is impaired relative to other indices, a possibility of DAT should be considered.

A clinician should consider and record (1) non-story intrusions in Logical Memory, (2) intrusions and transpositions in Verbal and Visual Paired Associates, (3) learning curve as revealed in Visual and Verbal Paired Associates I, and in the absence of a recognition extension, (4) the responses to probe questions following administration of Logical Memory II. While the utility of that information will be limited by the absence of normative values, the clinician will be assisted in forming a clinical impression over a number of administrations.

Differentiation of depressed individuals may be facilitated by grouping the subtests, or parts thereof, by the apparent amount of effortful processing required. For example, counting by 3's beginning with 1 requires more effortful processing than reciting the alphabet or counting backward from 20. Another example: it requires about 30 seconds to read each of the stories in Logical Memory I; attending to each story for 30 seconds, encoding, or attempting to encode, 50 information units presented in complex syntax (especially Story 1), and then organizing those information units encoded for a sustained verbal response would appear to demand more effortful processing than viewing a line drawing with 4 to 6 units of information for 10 seconds and reproducing the drawing. The Visual Paired Associates task of establishing a relationship between a figure and a colour, especially with verbal mediation, would appear to demand more effortful processing than the Verbal Paired Associates task in which half of the items already stand is some semantic relationship to each other (three by category and one by typical association).

David Wechsler and his organization seem to have a particular genius for developing instruments whose summary scores provide a good estimation of some general cognitive function, i.e., intelligence or memory, but which have limited value in differentiation of particular clinical groups. Witness the many studies attempting to find an Alzheimer's profile in the WAIS or WAIS-R subtest scores without success. However, substantial information that is of assistance in the clinical categorization of an individual's particular disorder can be obtained from the WAIS or WAIS-R by using a process approach as suggested by Edith Kaplan (1988). The closing comment is a clinical recommendation rather than clinical implication, and it is that a process approach be taken in the interpretation of the WMS-R when it is to be used to form a differential diagnostic impression. An entry into that process approach is suggested in the two preceding paragraphs.

IMPLICATIONS FOR FURTHER RESEARCH

Further Research on a DAT Memory Profile

The emergence of a "DAT profile" at statistically significant levels suggest that continued research into the nature of memory change in DAT is a legitimate pursuit. The accuracy of diagnosis of DAT on the basis of clinical

presentation range from 55% (Muller & Schwartz, cited in Wade et al., 1987) to 86% (Tierney et al., 1988). An accuracy of 59% with the WMS-R subtests found in this investigation is above the lower level reported, and while the clinical basis of the 55% to 86% accuracy of diagnosis is not reported, it is hoped that the diagnoses were not made on the basis of a single instrument.

It would be useful to have an instrument developed that collected those variables demonstrated to differentiate DAT from other memory disorders, i. e., interference and intrusion, learning curve, recency and primacy, recognition measures, response to cuing, and delayed vs. immediate recall. To a large extent the California Verbal Learning Test (CVLT) (Delis et al., 1987) incorporates those variables. There are, however, difficulties with the CVLT that become apparent in clinical practice. More impaired patients, and some frontal patients, tend to be "captured" by the notion of a "shopping list" and are confounded by their own shopping lists, which they appear to be unable to inhibit or which press upon them, and the items of the CVLT. And, the CVLT has no nonverbal measures; hence, nonverbal memory impairment DAT cannot be investigated with that measure.

Assessment of nonverbal memory impairment in DAT remains problematic. While there are a number of techniques of assessment of nonverbal memory that are useful, they tend to be separate instruments and are not incorporated into an instrument that measures both verbal and nonverbal abilities. The absence of the verbal measures creates a problem opposite to, but analogous to, that encountered with the CVLT; assessment of visual memory but not verbal memory for the same sample.

The weakness of the WMS-R subtests suggests that further research in to the "ecologically valid" assessment of visual or nonverbal memory is required. In the "real world" it is rare, outside an art classroom, that an individual is asked to look at something then draw it, or form an immediate association between a colour and a shape. The most common sign of visual or nonverbal memory impairment for DAT patients is the failure to *recognize* those persons, places, or things with which they are familiar or ought to be familiar. Further research is required to determine appropriate techniques to examine visual recognition memory as well as other nonverbal memory functions, e.g., recall of visual sequences and visual-motor learning and recall.

Further Research with the WMS-R

To a large extent the implications for further research have been outlined already. There is an urgent need to make the visual memory subtests more robust. When an instrument is described as intended for "evaluating the pattern and localization of organic brain damage" (Wechsler, 1987, p. 7), and it cannot find the missing temporal lobe (Loring, 1988) because the tests designed to make that determination are not adequate to the task, improvements are required. New visual tests and/or scoring changes are required which are sensitive to the differential recall of global (configural) and local (detail) elements if the test is to discriminate between right- and left-hemisphere impairments. Determining appropriate changes in designs and scoring will require considerable investigation.

Measurement of those variables demonstrated to select well between clinical groups and which are available in the existing WMS-R, i.e., non-story intrusions in logical Memory; intrusions and transpositions in Verbal Paired Associates and transpositions in Visual Paired Associates; learning curves for both Visual and Verbal Paired Associations; and recall with probe questions for Logical Memory II, should be standardized and age norms calculated. When the measures are standardized, their efficacy in differentiating clinical groups should be tested.

Finally, a set of recognition measures for the WMS-R should be developed and standardized by age group.

LIMITATIONS OF THE STUDY

Some of the limitations of this study are those inherent in any investigation of clinical populations in large medical facilities: records that cannot be recovered, missing data, lack of standardization in diagnostic labels, diagnoses from and physicians with varying expertise and interests.

Two important limitations arise with the DAT population. The first is the question of whether or not those patients identified as demential of an Alzheimer's type have Alzheimer's disease in the absence of pathological confirmation of the disease. That limitation is not unique to this study and is a limitation in most studies as relatively few DAT patients are followed to death and autopsied. Because the patients were drawn from a sample at a facility specializing in geriatric assessment and care, and many from a memory

clinic with a particular interest in investigation of memory disorders, it is most probable that the large proportion of those in the DAT groups conform to the NINCDS-ADRDA Work Group's criteria for the diagnoses of possible and probable DAT.

The second, and perhaps more important, limitation of the study is the failure to find the expected numbers of DAT patients in the patient population selected. On the basis of prevalence estimates, approximately one-half the patients referred for memory assessment should have been possible or probable DAT. As previously noted, it is anticipated, that the failure to find the expected numbers of DAT patients was the result of experienced geriatricians confidently diagnosing the more typical presentations of DAT on the basis of their own credible experience and without the assistance of a full neuropsychological assessment. Such patients would not have been available in the pool from which cases were drawn. The exclusion of those patients, if the surmise is correct, may have influenced the study in two ways. The "DAT profile" obtained may be a profile for atypical or less typical presentations of DAT. Alternatively, had those patients been included a more robust "DAT profile" may have been obtained. Despite these reservations, the results obtained are consistent with those obtained in other studies of DAT populations, and there is no compelling reason to suspect that the sample is not representative as many physicians with a divergence of experience and interests did refer individuals who they suspected of suffering an Alzheimer type dementia.

The last limitation to be noted has already been acknowledged. That limitation is this investigator's failure to specify in his hypotheses the level of accuracy of classification that would allow the question "Is there an Alzheimer's profile among the subtests of the Wechsler Memory Scale--Revised?" with a definitive "Yes" or "No". The best answer in the circumstances appears to be a "Yes, but . . ." answer: Yes, there is an Alzheimer's profile in the subtests, but as the instrument is presently constituted, the profile has limited diagnostic value.

REFERENCES

Aharon-Peretz, J., Cummings, J., & Hill, M. (1988). Vascular dementia and dementia of the Alzheimer type: Cognition, ventricular size, and leuko-araiosis. Archives of Neurology, 719-712.

Albert, M. S., Duffy, F. H., & McAnulty, G. B. (1990). Electrophysiologic comparisons between two groups of patients with Alzheimer's disease. Archives of Neurology, 47(8), 857-863.

Alfrey, A. C. (1986). Systemic toxicity of aluminum in man. Neurobioloby of Aging, 7(6), 543-545.

Alpérovitch, A., & Berr, C. (1988). Familial aggregation of dementia of Alzheimer type: Analysis from an epidemiological point of view. In P. M. Sinet, Y. Lamour, & Y. Christen (Eds.). Genetics and Alzheimer's disease(pp. 29-39). New York: Springer-Verlag.

American Psychiatric Association (1987). Diagnostic and statistical manual of mental disorders (3rd. ed. revised). Washington, D.C.: Author.

American Psychiatric Association (1994). Diagnostic and statistical manual of mental disorders (4rd. ed.). Washington, D.C.: Author.

Anderton, B. H. (1988). Genetics of Alzheimer's disease: Current status and future development of research. In P. M. Sinet, Y. Lamour, & Y. Christen (Eds.). Genetics and disease(pp. 29-39). New York: Springer-Verlag.

Bäckman, L., & Herlitz, A. (1990). The relationship between prior knowledge and face recognition memory in normal aging and Alzheimer's disease. Journals of Gerontology, 45(3), 94-100.

Backman, D. L., Wolf, P. A., Linn, R., Knoefel, J.E., Cobb, J., Belanger, A., D'Agostino, R. b., & White, L. R. (1992). Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. Neurology, 43, 115-119.

Baddeley, A. (1986). Working Memory. Oxford: Oxford University Press.

Baddeley, A. (1992). Working memory. Science, 255, 556-559.

Bannatyne, A. (1974). Diagnosis: A note on recategorization of the WISC scaled scores. Journal of Learning Disabilities, 1, 272-273.

Barclay, I., Zemcov, A., Blass, J. & Sansone, J. (1985). Survival in Alzheimer disease and vascular dementias. Neurology, 35, 834-840.

Barona, A. & Chastain, R. L. (1986) An Improved estimate of Premorbid IQ for Blacks and Whites. International Journal of Clinical Neuropsychology, 8(4), 169-172.

Barr, A., Benedict, R., Tune, L., & Brandt, J. (1992). Neuropsychological differentiation of Alzheimer's disease from vascular dementia. International Journal of Geriatric Psychiatry, 7, 621-627.

Bartus, R. T., Dean, R. L., Pontecorvo, M. J., & Flicker, C. (1985). The cholinergic hypothesis: A historical overview, current perspectives, and future directions. Annals of the New York Academy of Science, 444, 332-358.

Bayles, K. A., Boone, D. R., Tomoeda, C. K., Slauson, T. J., & Kaszniak, A. W. (1989). Differentiating Alzheimer's patients from normal elderly and stroke patients with aphasia. Journal Speech and Hearing Disorders, 54, 74-87.

Bayles, K. A., & Tomoeda, C. K. (1983). Confrontation naming impairment in dementia. Brain and Language, 19, 98-114.

Becker, J. T., Boller, R., Saxton, J., & McGonigle-Gibson, K. L. (1987). Normal rates of forgetting of verbal and non-verbal material in Alzheimer's disease. Cortex, 23, 59-72

Benson, D. F. (1988). PET/dementia: An update. Neurobiology of Aging, 9(1), 87-88.

Berg, L. (1988). Mild senile dementia of the Alzheimer type: diagnostic criteria and natural history. Mt. Sinai Journal of Medicine, 55, 87-96.

Berg, L., Danziger, W. L., Storandt, M., Coben, L. A., Gado, M., Hughes, C. P., Knesevich, J. W., & Botwinick, J. (1984). Predictive features in mild senile dementia of the Alzheimer type. Neurology, 34, 563-569.

Blackwood, D. H., St. Clair, D. M., Blackburn, I. M., & Tyrer, G. M. (1987). Cognitive brain potentials and psychological deficits in Alzheimer's dementia and Korsakoff's amnesic syndrome. Psychological Medicine, 17(2), 349-358.

Bonte, F. J., Ross, E. D., Chehabi, H. H., & Devous, M. D., Sr. (1986). SPECT study of regional cerebral blood flow in Alzheimer disease. Journal of Computer Assisted Tomography, 10, 579-583.

Borkowski., J. G., Benton, A. L., & Spreen, O. (1967). Word fluency and brain damage. Neuropsychologica, 5, 135-140.

Bornstein, R. A., & Chelune, G. J. (1988). Factor Structure of the Wechsler Memory Scale--Revised. Special issue: Initial validity studies of the new Wechsler Memory Scale--Revised. Clinical Neuropsychologist, 2(2), 107-115.

Bornstein, R. A., & Chelune, G. J. (1989). Factor structure of the Wechsler Memory Scale--Revised in relation to age and educational level. Archives of Clinical Neuropsychology, 4(1), 15-24.

Bornstein, R. A., Chelune, G. J., & Prifitera, A. (1989). IQ-memory discrepancies in normal and clinical samples. Psychological Assessment, 1(3), 203-206.

Bradley, W. G. (1990). Alzheimer's disease: Theories of causation. In T. Zandi & R. J. Ham (Eds.). New directions in dementia and Alzheimer's disease (pp. 31-38). New York: Plenum Press.

Brinkman, S. D., Largen, J. W., Gerganoff, S., & Pomara, N. (1983). Russell's Revised Wechsler Memory Scale in the evaluation of dementia. Journal of Clinical Psychology,39(6), 989-993.

Brun, A. (1989). Structural changes in aging and dementia of Alzheimer's type with special reference to recent etiologic and therapeutic theories. Progress in Clinical & Biological Research, 317, 285-293.

Bucht, G., Adolfsson, R., & Winblad, B. (1984). Dementia of the Alzheimer type and multi-infarct dementia: A clinical description and diagnostic problems. Journal of the American Geriatrics Society, 32, 491-498.

Budzenski, C. A. (1986). An analysis of memory dysfunction in senile dementia of the Alzheimer's type, multi-infarct dementia, and pseudodementia. Dissertation Abstracts International, 47, (4-B), 1713.

Burns, A., Philpot, M. P., Costa, D. C., Ell, P. J., & Levy, R. (1989). The investigation of Alzheimer's disease with single positron emission tomography. Journal of Neurology, Neurosurgery, and Psychiatry, 52, 248-253.

Butters, N., Granholm, E., Salmon, D. P., Grant, I., & Wolfe, J.(1987). Episodic and semantic memory: A comparison of amnesic and demented patients. Journal of Clinical and ExperimantalNeuropsychology, 9, 479-497.

Butters, N., Salmon, D. P., Cullum, C. M., Cairns, P., Tröster, A. J., Jacobs, D., Moss, M., & Cermak, L. S. (1988). Differentiation of amnesic and demented patients with the Wechsler Memory Scale--Revised. Special Issue: Initial validity studies of the new Wechsler Memory Scale--Revised. Clinical Neuropsychologist, 2(2), 133-148.

Capitani, E., Della Sala, S., & Spinnler, H. (1990). Controversial issues in Alzheimer's disease: Influence of onset-age and hemispheric asymmetry of impairment. Cortex, 26(1), 133-145.

Chase, T. N., Foster, N. L., Fedio, P., Brooks, R., Mansi, L., & DiChiro, G. (1984). Regional cortical dysfunction in Alzheimer's disease as determined by positron emission tomography. Annals of Neurology, 15(suppl), S170-S174.

Chelune, G. J., & Bornstein, R. A. (1988). WMS-R patterns among patients with unilateral brain lesions. Special Issue: Initial validity studies of the new Wechsler Memory Scale--Revised. Clinical Neuropsychologist,2(2), 121-132.

Chertkow, H., & Bub, D. (1990). Semantic memory loss in dementia of Alzheimer's type: What do various measures measure? Brain, 113,(2), 397-417.

Chui, H. C., Teng, E. L., Henderson, V. W., & Moy, A. C. (1985). Clinical subtypes of dementia of the Alzheimer type. Neurology, 35, 1544-1550.

Cohen, G. D. (1988). The brain in human aging. New York: Springer Publishing.

Coyne, A. C., Liss, L., & Geckler, C. (1990). The relationship between cognitive status and verbal information processing. Journal of Gerontology, 39(6), 711-717.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. Journal of Verbal Learning and Verbal Behavior, 11, 671-684.

Crapper McLachlan (1986). Aluminum and Alzheimer's disease. Neurobiology of Aging, 7(6), 525-532.

Crystal, H., Dickson, D., Fuld, P., Masur, D., Scott, R., Mehler, M., Masdeu, J., Kawas, C., Aronson, M., & Wolfson, L. (1988). Clinico-pathological studies in dementia: Nondemented subjects with pathologically confirmed Alzheimer's disease, Neurology, 38, 1682-1687.

Cullum, C. M., Butters, N., Tröster, A. I., & Salmon, D. P. (1990). Normal aging and forgetting rates on the Wechsler Memory Scale--Revised. Archives of Clinical Neuropsychology, 5(1), 23-30.

Cummings, J. L., & Benson, F. (1988). Psychological dysfunction accompanying subcortical dementias. Annual Review of Medicine 39, 53-61.

Cummings, J. L., Benson, D. F., Hill, M. A., & Read, S. (1985). Aphasia in dementia of the Alzheimer type. Neurology, 35, 394-397.

Cummings, J. L., Miller, B., Hill., M. A., & Neshkes, R. (1987). Neuropsychiatric aspects of multi-infarct dementia and dementia of the Alzheimer type. Archives of Neurology, 44, 389-393.

Davis, K. L., Thal, L. J., Gamzu, E. R., Davis, C. S., Woolson, R. F., Gracon, S. I., Drachman, D. A., Schneider, L. S., Whitehouse, P. J., Hoover, T. M., Morris, J. C., Kavdas, C. H., Knopman, D. S., Earl, N. S., Kumar, V., Doody, R. S., & the Tacrine Collaborative Study Group (1992). A doouble blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The New England Jouranl of Medicine, 327,(18), 473-479.

Davis, P. E., & Mumford, S. J. (1984). Cued recall and the nature of memory disorders in dementia. British Journal of Psychiatry, 144, 383-386.

D'Lia, L., Satz, P., & Schretlen, D. (1989). Wechsler Memory Scale: A critical appraisal of the normative studies. Journal of Clinical & Experimental Neuropsychology, 11(4), 551-568.

Delis, D. C., Massman, P.J., Butters, N., Salmon, D. P., Shear, P. K., Demadura, T., & Filoteo (1992). Spatial cognition in Alzheimer's disease: Subtypes of global-local impairment. Journal of Clinical and Experimental Psychology, 14(4), 463-477.

DesRosiers, G. (1992). Primary or depressive dementia: Clinical features. International Journal of Geriatric Psychiatry, 7, 629-638.

Erickson, K. R. (1990). Amnestic disorders: Pathophysiology and patterns of memory dysfunction. Western Journal of Medicine, 152, 159-166.

Eslinger, P. J., & Damasio, A. R. (1986). Preserved motor learning in Alzheimer's disease: Implications for anatomy and behavior. Journal of Neuroscience, 6, 3006-3009.

Evans, D. A., Funkenstein, H., Albert, M. S., Scherr, P. A., Cook, N. R., Chown, M. J., Hebert, L. E., Hennekens, C. H., Taylor, J. O. (1989). Prevalence of Alzheimer's disease in a community population of older persons: Higher than previously reported. Journal of the American Medical Association, 262, 2551-2556.

Farlow, M., Ghetti, B., Benson, M. D., Farrow, J. S., Van Nostrand, W. E., & Wagner, S. L. (1992). Low cerebrospinal-fluid concentrations of soluble amyloid ß-protein precursor in hereditary Alzheimer's disease. Lancet, 340, 453-545.

Farlow, M., Gracon, S. I., Hereshey, L. A., Lewis, K. W., Sadowsky, C. H., & Dolan-Ureno J. for the Tacrine Study Group (1992). A controlled trial of tacrine in Alzheimer's disease. Journal of the American Medical Association, 266, 2523-2530.

Folstein, M. F., Warren, A., & McHugh, P. R. (1988). Hetrogeneity in Alzheimer's disease: An exercise in the resolution of phenotype. In P. M. Sinet, Y. Lamour, & Y. Christen. (Eds.) Genetics and Alzheimer's disease, (pp 5-12). New York: Springer-Verlag.

Fopma-Loy, J. (1986). Depression & dementia: Differential diagnosis. Journal of Psychosocial Nursing & Mental Health Services, 24(2), 27-29.

Freedman, M., & Oscar-Berman, M. (1987). Tactile discrimination learning deficits in Alzheimer's and Parkinson's diseases. Archives of Neurology, 44(4), 394-398.

Galasko, D., Kwo-on-Yuen., P. F., Klauber, M. R., & Thal, L. J. (1990). Neurological findings in Alzheimer's disease and normal aging. Archives of Neurology, 47, 625-627.

Gandolfo, C., Vecchia, R., Moretti, C., Brusa, G., Scotto, P. (1986). WAIS testing in degenerative and multi-infarct dementia. Acta Neurologica, 8(1), 45-50.

Gandy, S., & Greengard, P. (1992) Amyloidogenesis in Alzheimer's disease: Some possible therapeutic opportunities. Trends in Pharmacological Sciences 13, 108-113.

Gautrin, D., Froda, S., Tetreault, H., & Gauvreau, D. (1990). Canadian projections of cases suffering from Alzheimer's disease and senile dementia of Alzheimer type over the period of 1986 - 2031. Canadian Journal of Psychiatry, 35(2), 162-165.

Gentleman, (1992). Alzheimer's disease and βA4: Getting to the core of the problem. Trends in Neurosciences, 15(9), 315-316.

George, A. E., de Leon, M. J., Stylopoulos, L. A., Miller, J., Kluger, A., Smith, G., & Miller, D. C. (1990). CT diagnostic features of Alzheimer disease: Importance of the choroidal hippocampal fissure complex. American Journal of Neuroradiology, 11, 101-107.

Ghetti, G., & Bugiani, O. (1986). "Aluminum disease" and Alzheimer's disease. Neurobiology of Aging, 7(6), p. 536.

Grober, E., & Buschke, H. (1987). Genuine memory deficits in dementia. Developmental Neuropsychology, 3, 13-36.

Gustafson, L., & Nilsson, L. (1982). Differential diagnosis of presenile dementia on clinical grounds. Acta Psychiatrica Scandinavia, 65194-209.

Hachinski, V. C. (1978). Cerebral blood flow: Differentiation of Alzheimer's disease from multi-infarct dementia. Aging, 7, 97-103.

Hagberg, B., & Gustafson, L. (1985). On diagnosis of dementia: Psychometric investigation and clinical psychiatric evaluation in relation to verified diagnosis. Archives of Gerontology and Geriatrics, 4, 321-332.

Hardy & Allsop (1991). Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends in Pharmacological Sciences, 12(10), 383-388.

Hardy, J. A., Mann, D. M., Wester, P., & Winblad, B. (1986). An integrative hypothesis concerning the pathogenesis and progression of Alzheimer's disease. Neurobiology of Aging, 7(6), 489-502.

Hart, R. P., Kwentus, J. A., Taylor, J. R., & Harkins, S. W. (1987). Rate of forgetting in dementia and depression. Journal of Consulting & Clinical Psychology, 55(1), 101-105.

Hart, R. P., Kwentus, J. A., Wade, J. B., & Hamer, R. M. (1987). Digit symbol performance in mild dementia and depression. Journal of Consulting and Clinical Psychology, 55, 236-238.

Hauw, J.-J., Duyckaerts, P., Delaère, & Piette, F. (1990). Topography of lesions in Alzheimer's disease: A challenge to morphologists. In S. R. Rapoport, H. Petit, D. Leys, & Y. Christen (Eds.), Imaging, cerebral topography and Alzheimer's disease (pp. 53-67). New York: Springer-Verlag.

Haxby, J. (1990). Cognitive deficits and local metabolic changes in dementia of the Alzheimer type. In S. R. Rapoport, H. Petit, D. Leys, & Y. Christen (Eds.), Imaging, cerebral topography and Alzheimer's disease (pp. 109-119). New York: Springer-Verlag.

Heindel, W. C., Salmon, D. P., Shults. C. W., Walicke, P. A., & Butters, N. (1989). Neuropsychological evidence for multiple implicit memory systems: A comparison of Alzheimer's, Huntingtons' and Parkinson's. The Journal of Neuroscience, 9, 582-587.

Helkala, E. L., Laulumaa, V., Soininen, H., & Riekkinen, P. J. (1989). Different error patterns of episodic and semantic memory in Alzheimer's disease and Parkinson's disease with dementia. Neuropsychologia, 27(10), 1241-1248.

Herman, D. O. (1988). Development of the Wechsler Memory Scale--Revised. The Clinical Neuropsychologist, 2(2), 107-115.

Hier, D. B., Hagenlocker, K., & Shindler, A. G. (1985). Language disintegration in dementia: Effects of etiology and severity. Brain & Language, 25,(1), 117-133.

Huber, S. J., & Paulson, G. W. (1985). The concept of subcortical dementia. American Journal of Psychiatry, 142(11), 1312-1317.

Huff, F. J., Corkin, S., & Growdon, J. H. (1986). Semantic impairment and anomia in Alzheimer's disease. Brain and Language, 28, 235-249.

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. British Journal of Psychiatry, 140, 566-572.

Jacobs, D., Tröster, A. I., Butters, N., Salmon, D. P., & Cermak, L. S. (1990). Intrusion errors on the Visual Reproduction Test of the Wechsler Memory Scale and the Wechsler Memory Scale--Revised: An analysis of demented and amnesic patients. Clinical Neuropsychologist, 4(2), 177-191.

Jagust, W. J., Davies, P., Tiller-Borcich, J. K., & Reed, B. R. (1990). Focal Alzheimer's disease. Neurology, 40, 14-19.

Jagust, W. J., Reed, B. R., Seab, J. P., & Budinger, T. F. (1990). Alzheimer's disease: Age at onset and single-photon computed tomographic patterns of regional cerebral blood flow. Archives of Neurology, 47, 628-633.

Jenike, M. A., Albert, M. S., Heller, H., Gunther, J., & Goff, D. (1990). Oral physostigmine treatment for patients with presenile and senile dementia of the Alzheimer type: A double-blind placebo-controlled trial. Journal of Clinical Psychiatry, 51(1), 3-7.

Judd, B. W., Meyer, J. S., Rogers, R. L., Gandhi, S., Tanahashi, N., Mortel, K., & Tawaklna, T. (1968). Cognitive performance correlates with cerebrovascular impairments in multi-infarct dementia. Journal of the American Geriatrics Society, 34(5), 355-360.

Kaplan, E. (1988). A process approach to neuropsychological assessment. In Boll, T., & Bryandt, B. K. (Eds.) Clinical Neuropsychology and Brain Function: Research, Measurement, and Practice (pp. 127-167). Washington, D. C.: American Psychological Association.

Kaszniak, A. W. (1988). Cognition in Alzheimer's disease: Theoretical models and clinical implications. Neurobiology of Aging, 9, 92-94.

Kaufman, A. S. (1979). Intelligent testing with the WISC-R. New York: Wiley & Sons.

Kerlinger, F. N. (1973). Foundations of behavioral research (2nd ed.). Toronto: Holt, Rinehart and Winston, Inc.

Khachaturian, Z. S. (1986). Aluminum toxicity among other views on the etiology of Alzheimer's disease. Neurobiology of Aging, 7(6), 537-539.

Kirshner, H. S., Webb, W. G., & Kelly, M. P. (1984). The naming disorder of dementia. Neuropsychologia, 22, 23-30.

Knopman, D. S., Mastri, A. R., Frey, W. H., Sung, J. H., & Rustan, T. (1990). Dementia lacking distinctive histologic features: A common non-Alzheimer dementia. Neurology, 40(2), 251-256.

Knotek, P., Bayles, K., & Kaszniak, A. (1990). Response consistency on a semantic memory task in persons with dementia of the Alzheimer type. Brain and Language, 38, 465-475.

Kobari, M., Meyer, J. S., & Ichijo, M. (1990). Leuko-araiosis, cerebral atrophy and cerebral perfusion in normal aging. Archives of Neurology, 47, 161-165.

Kontiola, P., Laaksonen, R, Sulkava, R., & Erkinjuntti, T. (1990). Pattern of language impairment is different in Alzheimer's disease and multi-infarct dementia. Brain & Language, 38(3), 364-384.

Kopelman, M. D. (1985). Rates of forgetting in Alzheimer-type dementia and Korsakoff's syndrome. Neuropsychologia, 23, 623-638.

Kraus, A. S., & Forbes, W. F. (1992). Aluminum, floride, and the prevention of Alzheimer's disease. Canadian Journal of Public Health, 83(2), 97-100.

La Rue, A. (1982). Memory loss and aging: Distinguishing dementia from benign senescent forgetfulness and depressive pseudodementia. Psychiatric Clinics of North America, 5, 89-103.

Liston, E. H. (1979). Clinical findings in presenile dementia: A report of 50 cases. Journal of Nervous and Mental Diseases, 167, 337-342.

Liston, E., & La Rue, A. (1983a). Clinical differentiation of primary degenerative and multi-infarct dementia: A critical review of the evidence. Part I: Clinical studies. Biological Psychiatry, 18, 1451-1465.

Liston, E., & La Rue, A. (1983b). Clinical differentiation of primary degenerative dementia and multi-infarct dementia: A clinical review of the evidence, Part II: Pathological studies. Biological Psychiatry, 18, 1467-1484.

Lockhart, R. S., & Craik, F. I. (1990). Levels of processing: A retrospective commentary on a framework for memory research. Canadian Journal of Psychology, 44(1), 87-112.

Loring, D. W. (1989). The Wechsler Memory Scale--Revised, or the Wechsler Memory Scale--Revisited? Clinical Neuropsychologist, 3, 59-69.

Loring, D. W., Lee, G. P., Martin, R. C., & Meador, K. J. (1989). Verbal and Visual Memory Index discrepancies from the Wechsler Memory Scale--Revised: Cautions in interpretation. Psychological Assessment, 1(3), 198-202.

Mackenzie, T. B., Robiner, W. N., & Knopman, D. S. (1989). Differences between patient and family assessments of depression in Alzheimer's disease. American Journal of Psychiatry, 146(9), 1174-1178.

Maina, G., Fiori, L., Torta, R., Fagiani, M. B., Ravizza, E., Bonavita, E., Ghiazza, B., Teruzzi, F., Zagnoni, P., Ferrario, E., Belloni, G., Tassi, G., Inzoli, M., Lombardi, G., Voltolini, G., Gherardi, G., Martinazzoli, A., Straneo, U., Bernini, P., Mazzocchi, P., Belloni, G., Soldati, M., Stramba-Badiale, M., Castoldi, C., Rossi, F., Balladore, G., & Macciolli, D. (1989). Oxiracetam in the treatment of primary degenerative and multi-infarct dementia: A double-blind, placebo-controlled study. Neuropsychobiology, 21(3), 141-145.

Martin, A., Brouwers, P., Cox, C., & Fedio, P. (1985). On the nature of the verbal memory deficit in Alzheimer's disease. Brain and Language, 25, 323-341.

Martin, A., Brouwers, P., Lalonde, F., Cox, C., Teleska, P., Fedio, P., Foster, N. L., & Chase, T. N. (1986). Toward a behavioral typology of Alzheimer's patients. Journal of Experimental and Clinical Neuropsychology, 8, 594-610.

Martin, A., & Fedio, P. (1983). Word production and comprehension in Alzheimer's disease: The breakdown of semantic knowledge. Brain and Language, 19, 124-141.

Mosla, P., Paljarvi, L., & Rinne, J., Rinne, U. Sako, E. (1985). Validity of clinical diagnosis in dementia: A prospective clinicopathological study. Journal of Neurological and Neurosurgical Psychiatry, 48, 1085-1090.

McCue, M., Goldstein, G., & Shelly, C. (1989). The application of a short form of the Luria-Nebraska Neuropsychological Battery to discrimination between dementia and depression in the elderly. International Journal of Clinical Neuropsychology, 11(1), 21-29.

McGeer, E. G., Peppard, R. P., McGeer, P. L., Tuokko, H., Crockett, D., Parks, R., Akiyama, H., Calne, D. B., Beattie, B. L., & Harrop, R. (1990). ^{18}Fluorodeoxyglucose positron emission tomography studies in presumed Alzheimer cases, including 13 serial scans. The Canadian Journal of Neurological Science, 17, 1-11.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology, 34, 939-944.

Merriam, A. E., Aronson, M. K., Gaston, P., Wey, S., & Katz, I. (1988). The psychiatric symptoms of Alzheimer's disease. Journal of the American Geriatrics Society, 36, 7-12.

Mitrushina, M., Satz, P., & Van Gorp, W. G. (1989). Some putative cognitive precursors in subjects hypothesized to be at risk for dementia. Archives of Clinical Neuropsychology, 4(4), 323-333.

Mohr, E., Litvan, I., Williams, J., Fedio, P., & Chase, T. N. (1990). Selective deficits in Alzheimer and parkinsonian dementia: Visuospatial function. Canadian Journal of Neurological Science, 17(3), 292-297.

Morris, R. G. (1986). Short-term forgetting in senile dementia of the Alzheimer's type. Cognitive Neuropsychology, 3, 77-97.

Morris, R. G. (1987). Articulatory rehearsal in Alzheimer type dementia. Brain and Language, 30, 351-362.

Morris, R. G., & Baddeley, A. D. (1988). Primary and working memory functioning in Alzheimer-type dementia. Journal of Clinical and Experimental Neuropsychology, 10, 279-296.

Morris, R. G., & Kopelman, M. D. (1986). The memory deficits in Alzheimer-type dementia: A review. The Quarterly Journal of Experimental Psychology, 38, 575-602.

Morris, R., Wheatley, J., & Britton, P. (1983). Retrieval from long-term memory in senile dementia: Cued recall revisted. British Journal of Clinical Psychology, 22, 141-142.

Neary, D., Snowden, J. S., Bowen, D. M., Sims, N. R., Northern, B., Yates, P., & Davison, A. (1986). Neuropsychological syndromes in presenile dementia due to cerebral atrophy. Journal of Neurology, Neurosurgery, & Psychiatry, 49,(2), 163-174.

Neary, D., Snowden, J. S., Mann, D. M., Bowen, D. M., Sims, N. R., Northen, B., Yates, P. O., & Davison, A. N. (1986).Alzheimer's disease: A correlative study. Journal of Neurology, Neurosurgery, & Psychiatry, 49(3), 229-237.

Nebes, R. D., & Brady, C. B. (1988). Integrity of semantic fields in Alzheimer's disease. Cortex, 24(2), 291-299.

Nebes, R. D., Boller, F., & Holland, A. (1986). Use of semantic context by patients with Alzheimer's disease. Psychology and Aging, 1(3), 261-269.

Nebes, R. D., Martin, D. C., & Horn, L. C. (1984). Sparing of semantic memory in Alzheimer's disease. Journal of Abnormal Psychology, 93(3), 321-330.

Ober, B. A., Dronkers, N. F., Koss, E., Delis, D. C., & Friedland, R. P. (1986). Retrieval from semantic memory in Alzheimer-type dementia. Journal of Clinical and Experimental Neuropsychology, 8, 75-92.

O'Brien, J. T., Beats, B., Hill, K., Howard, R., Sahakian, B., & Levy, R. (1992). Do subjective memory complaints precede dementia? A three-year follow-up of patients with supposed 'benign senescent forgetfulness.' International Journal of Geriatric Psychiatry, 7, 481-486.

O'Grady, K. E. (1988). Convergent and discriminant validity of Russell's Revised Wechsler Memory Scale. Personality & Individual Differences, 9(2), 321-327.

Palmert, M. R., Usiak, M., Mayeux, R., Raskind, M., Tourtellotte, W.W., & Younkin, S. G. (1990). Soluble derivatives of the ß amyloid protein precursor in cerebrospinal fluid: Alterations in normal aging and in Alzheimer's disease. Acta Neurologica Scandinavica, 85, 343-346.

Parlato, V., Carlomagno, S., Merla, F., & Bonavita, V. (1988). Patterns of verbal memory impairment in dementia: Alzheimer's disease versus multi-infarctual dementia. Acta Neurologica, 10(6), 343-351.

Pepin, E. P., & Eslinger, P. J. (1989). Verbal memory decline in Alzheimer's disease: A multiple-processes deficit. neurology, 39(11), 1477-1482.

Pericak-Vance, M. A., Yamaoka, L. H., Haynes, C. S., Speer, M. C., Haines, J. L., Gaskell, P. C., Hung, W.-Y., Clark, C. M., Heyman, A. L., Trofatter, J. A., Eisenmenger, J. P., Gilbert, J. R., Lee, J. E., Alberts, M. J., Dawson, D. V., Bartlett, R. J., Earl, N. L., Siddique, T., Vance, J. M., Conneally, P. M., & Roses, A. D. (1988). Genetic linkage studies in Alzheimer's disease families. Experimental Neurology, 102, 271-279.

Peterson, R. C., Smith, G., Kokmen, E., Ivnik, R. J., & Tangalos, E. G. (1992). Memory function in normal aging. Neurology, 42, 396-401.

Petry, S., Cummings, J. L., Hill, M. A., Shapira, J. (1989). Personality alterations in dementia of the Alzheimer type: A three-year follow-up study. Journal of Geriatric Psychiatry and Neurology, 2(4). 203-207.

Pettegrew (1986). Aluminum and Alzheimer's disease: An evolving understanding. Neurobiology of Aging, 7(6), 539-543.

Poitrenaud, J., Moy, F., Girousse, A., Wolmark, Y., & Piette, F. (1989). Psychometric procedures for analysis of memory loss in the elderly. Archives of gerentological Gericatrics, Suppl. 1, 173-183.

Poirier, J., Davignon,, J., Bouthillier, D., Kogan, S., Bertrand, P., & Gauthier, S. (1993). Apolipoprotein E polymorphism and Alzheimer's disease. The Lancet, 342, 697-699.

Poon, L. W. (1985). Differences in human memory with aging: Nature, causes, and clinical implications. In J. E. Birren & K. W. Schaie (Eds.). Handbook of the psychology of aging (pp. 427-462). New York: Van Nostrand Reinhold Co.

Prigatano, G. P. (1978). Wechsler Memory Scale: A selective review of the literature. Archives of the Behavioral Sciences, 54, 3-19.

Rapcsak, S. Z., Arthur, S. A., Bliklen, D. A., & Rubens, A. B. (1989). Lexical Agraphia in Alzheimer's disease. Archives of Neurology, 45, 65-68.

Rapoport, S. I. (1988). A phylogenetic hypothesis for Alzheimer's disease. In P. M. Sinet, Y. Lamour, & Y. Christen (Eds.). Genetics and Alzheimer's disease (pp. 62-88). New York: Springer-Verlag.

Rapoport, S. I. (1990). Topography of Alzheimer's disease: Involvement of Association neocortices and connected regions; pathological, metabolic and cognitive correlations; relation to evolution. In S. R. Rapoport, H. Petit, D. Leys, & Y. Christen (Eds.), Imaging, cerebral topography and Alzheimer's disease (pp. 1-17). New York: Springer-Verlag.

Regland, B., & Gottfries, G.-H. (1992). The role of amyloid ß-protein in Alzheimer's disease. The Lancet, 340, 467-496.

Roid, G. H., Prifitera, A., & Ledbetter, M. (1988). Confirmatory analysis of the structure factor of the Wechsler Memory Scale-Revised. Special Issue: Initial validity studies of the new Wechsler Memory Scale--Revised. Clinical Neuropsychologist,2(2), 116-120.

Román, G.C. (1987). Senile dementia of the Binswanger type. Journal of the American Medical Association, 258(13), 1782-1788.

Rosen, W. G. (1980). Verbal fluency in aging and dementia. Journal of Clinical Neuropsychology, 2(2), 135-146.

Rubin, E. H., & Kinschert, D. A. (1989). Psychopathology of very mild dementia of the Alzheimer type. American Journal of Psychiatry, 1456(8), 1017-1021.

Rubin, E. H., Morris, J. C., Grant, E. A., & Vendegena, T. (1989). Very mild senile dementia of the Alzheimer type: I. Clinical assessment. Archives of Neurology, 46, 379-382.

Sattler, J. M. (1982). Assessment of children's intellignece and special abilities (2nd ed.). Boston: Allyn and Bacon Inc.

Sahakian, B., Jones, G., Levy, R., Gray, J., & Warbuton, D. (1989). The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. British Journal of Psychiatry, 154, 797-800.

Sahakian, B. J., Morris, R. G., Evenden, J. L., Heald, A., Levy, R., Philpot, M., & Robbins, T. W. (1988). A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain, 111, 695-718.

Saunders, A. M., Schmader, K., Breitner, J. C., Benson, M. D., Brown, W. T., Goldfarb, D., Manwaring, M. G., Szymanski, M. H., McCown, N., Dole, K. C., Schmechel, D. E., Strittmatter, W. J., Pericak-Vance, M. A., & Roses, A. D. (1993). Apolipoprotein ε4 allele distributions in late-onset Alzheimer's disease and other amyloid-forming diseases. The Lancet, 342, 710-711.

Selkoe, D. J. (1990). Deciphering Alzheimer's disease: The amyloid precursor protein yields new clues. Science, 248,1058-1060.

Selkoe, D. J. (1991). In the beginning . . .. Nature, 432-433.

Shuttleworth, E. C., & Huber, S. J. (1988). A longitudinal study of the naming disorder of dementia of the Alzheimer type. Neuropsychiatry, Neuropsychology, & Behavioral Neurology, 1(4), 267-282.

Shuttleworth, E. C., & Huber, S. J. (1989). The picture absurdities test in the evaluation of dementia. Brain & Cognition, 11(1), 50-59.

Sisodia, S. S., Koo, E. H., Beyreuther, K., Unterbeck, A., & Price, D. L. (1990). Evidence that ß-Amyloid protein in Alzheimer's disease is not derived by normal processing. Science, 248, 492-495.

Smith, G., Ivnik, R. J., Peterson, R. C., Malic, J. F., Kokmen, E., & Tangalos, E. (1991). Age-associated memory impairment diagnosis: Problems of reliability and concerns for terminology. Journal of the American Psychological Association, Inc., 6(4), 551-558

Spinnler, H., & Della Sala, S. (1988). The role of clinical neuropsychology in the neurological diagnosis of Alzheimer's disease. Journal of Neurology, 235, 258-271.

SPSS (1993). SPSS for Windows; Release 6, SPSS Inc.

St. George-Hyslop, P. H., Tanzi, R. E., Polinsky, R. J., Haines, J. L., Nee, L., Watkins, P. C., Meyers, R. H., Feldman, R. G., Pollen, D., Drachman, E., Amaducci, L., Sorgi, S., Placentini, S., Stewart, G. D., Hobbs, W., Conneally, P. M., & Gusella, J. F. (1987). The genetic defect causing familial Alzheimer's disease maps on chromosome 212. Science, 235, 885-890.

Storandt, M., Botwinick, J., Danziger, W., Berg, L., & Hughes, C. (1984). Psychometric differentiation of mild senile dementia of the Alzheimer type. Archives of Neurology, 41, 497-499.

Storandt, M., & Hill, R. D. (1989). Very mild senile dementia of the Alzheimer type: II Psychometric test performance. Archives of Neurology, 46, 383-386.

Teri, L., Hughes, J.P., & Larson, E. B. (1990). Cognitive deterioration in Alzheimer's disease: Behavioral and health factors. Journal of Gerontology: Psychological Sciences, 45(2), 58-63.

Teri, L., Borson, S., Kiyak, H. A., & Yamagishi, M. (1989). Behavioral disturbance, cognitive dysfunction, and functional skill: Prevalence and relationship in Alzheimer's disease. Journal of the American Geriatrics Society, 37,(2), 109-116.

Terry, R. D., & Katzman, R. (1983). Senile dementia of the Alzheimer type. Annals of Neurology, 14(5), 497-506.

Thal, L. J., Grundman, M., & Klauber, M. R. (1988). Dementia: Characteristics of a referral population and factors associated with the progression. Neurology, 38(7), 1083-1090.

Tierney, M. C., Fisher, R. H., Lewis, A. J., Zorzitto, M. L., Snow, W. G., Reid, D. W., & Nieuwstraten, P. (1988). The NINCDS-ADRDA work group criteria for the clinical diagnosis of probable Alzheimer's disease: A clinicopathologic study of 57 cases. Neurology, 38, 359-364.

Urakami, K., Takahaski, K., Saito, H., Okada, A., Nakamura, S., Tanaka, S., Kitaguchi, N., Tokushima, Y., & Yamamoto, S. (1992). Amyloid ß protein precursors with Kunitz-type inhibitor damanis and acetylcholineasterase in cerebrospinal fluid from patients with dementia of the Alzheimer type. Acta Neurologica Scandinavica, 85, 343-346.

Van Nostrand, W. E., Wagner, S. L., Haan, J., Bakker, E., & Roos, R. A. (1992). Alzheimer's disease and hereditary Cerebral Hemorrhage with amyloidosis-Dutch type share a decrease in cerebrospinal fluid levels of amyloid ß-protein precursor. Annals of Neurology, 32, 215-218.

Villardita, C., Grioli, S., Lomeo, C., Cattaneo, C., & Parini, J. (1992). Clinical studies with oxiracetam in patients with dementia of Alzheimer type dementia and multi-infarct dementia of mild to moderate degree. Neuropsychobiology, 25, 24-28.

Vitaliano, P. P., Breen, A. R., Albert, M.S., Russo, J., & Prinz, P. (1884). Memory, attention, and functional status in community-residing Alzheimer-type dementia patients and optimally healthy aged individuals. Journal of Gerontology, 39, 58-64.

Wade, J. P. H., Mirsen, T. R., Hachinski, V. C., Fisman, M., Lau, C., & Merskey, H. (1987). The clinical diagnosis of Alzheimer's disease. Archives of Neurology, 44, 24-29.

Waldemar, G., Paulson, O., & Lassen, N. (1990). Brain imaging with SPECT in Alzheimer's disease. In S. R. Rapoport, H. Petit, D. Leys, & Y. Christen (Eds.), Imaging, cerebral topography and Alzheimer's disease (pp. 139-144). New York: Springer-Verlag.

Wechsler, D. A. (1981). Wechsler Adult Intelligence Scale--Revised Manual. New York: Psychological Corporation.

Wechsler, D. A. (1987). Wechsler Memory Scale--Revised Manual. New York: Psychological Corporation.

Whelihan, W. M., & Lesher, E. L. (1985). Neuropsychological changes in frontal functions with aging. Developmental Neuropsychology, 1(4), 371-380.

Wilson, S. W., Bacon, L. D., Kramer, R. L., Fox, J. H., & Kasniak, A. W. (1983). Word frequency effect and recognition memory in dementia of the Alzheimer type. Journal of Clinical Neuropsychology, 5(2), 97-104.

Wisniewski, H. M., Moretz, R. C., & Iqbal, K. (1986). No evidence for aluminum in etiology and pathogenesis of Alzheimer's disease. Neurobiology of Aging, 7(6), 532-535.

Wragg, R. E., & Jeste, D. V. (1989). Overview of depression and psychosis in Alzheimer's disease. American Journal of Psychiatry, 146(5), 577-587.

Zubenko, G., Moossy, J., & Kopp, U. (1990). Neurochemical correlates of major depression in primary dementia. Archives of Neurology, 47, 209-214.

APPENDIX 1

CONTENT AND TASK ANALYSIS OF WMS-R SUBTESTS

Information and Orientation Questions

Content

Personal biographical information:
With the exception of current age, required information is largely overlearned and unchanging; current age requires yearly updating.
Information is semantic/verbal.
Current/recent public information:
Information that requires periodic updating (new learning); period of updating varies with date of administration of test relative to elections, and may vary from days to as many as 8 years.
Information is semantic/verbal; some elements may be episodic/verbal
Orientation questions:
Information that requires hourly, daily, and monthly updating for temporal questions; information for place is highly variable depending on patient's circumstances, e.g., level of consciousness on admission to facility, length of residence in community, etc.

Information is episodic/verbal.

Task

Recall and verbally present correct answers.

Basic cognitive requirements:

Ability to attend to and comprehend task requirements; incidental and conscious attention to ongoing flow of events, awareness of environment; basic comprehension of oral language; ability to respond orally; ability to attend in immediate environment.

Memory requirements:

Recall of remote, overlearned, unchanging semantic/verbal information.
Recall of long-term/remote episodic/verbal information requiring periodic updating.

Factors contributing to poor performance

Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Social/cultural isolation
Aphasic disorders
Amnestic disorders

SUBTESTS OF ATTENTION/CONCENTRATION, VERBAL, VISUAL, AND GENERAL MEMORY INDEXES

Mental Control

Content

(1) Counting backward from 20; (2) recitation of English alphabet; and (3) adding by 3s beginning with 1; all within time constraints. Information is semantic/verbal.

Tasks

(1) count backward from 20-1 aloud in 30 seconds; (2) recite alphabet in 30 seconds; and (3) count, aloud, to 40 by 3s beginning with '1'.

Basic cognitive requirements:

Ability to attend to and comprehend task requirements; ability to make an oral response; ability to count to 20; ability to recite English alphabet; ability to add a single digit number to other single and double digit numbers; ability to process and respond within time constraints (adequate processing speed); functional automatic and controlled processing; mental flexibility; inhibition of irrelevant information; ability to sequence in predetermined/prescribed order; ability to monitor and modify performance.

Memory requirements:

Recall of remote overlearned declarative/semantic/verbal information; recall of numbers and number sequence 1-20, recall of English alphabet.

Recall of procedural/semantic/verbal information; elementary mathematical operation.

Recall of immediate episodic information; recall of last number recited in counting backward and adding; recall of last letter recited.

Factors contributing to poor performance

Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Social/cultural/educational deprivation
Aphasic disorders
Amnestic disorders
Mental retardation

Figural Memory

Content

Linear "abstract designs": 3.8 x 4.5cm rectangles divided interiorly in to 4 to 12 smaller light grey, dark grey, and white squares or rectangles. One to three stimulus rectangles and 3 to 9 recognition rectangles. Information is episodic/figural.

Task

(1) learn the pattern of one stimulus rectangle in 5 seconds, and identify that rectangle from among three rectangles, one identical and two distractors.

(2) learn the patterns of three stimulus rectangles in 15 seconds, and identify those rectangles from among nine rectangles, three identical and six distractors.

Basic Cognitive Requirements

Ability to attend to and comprehend task requirements; ability to attend to figural stimuli; ability to perceive spatial relations; ability to perceive visual detail; ability to perceive figure-ground relationships; ability to divert and refocus attention; ability to monitor and modify performance; adequate visual processing speed.

Memory Requirements

Recognition of visual-spatial patterns.
Recognition is immediate/declarative/episodic/figural.

Factors Contributing to Deficit Performance

Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Amnestic disorders
Right- or left-hemisphere dysfunction
Specific visual learning disability

Logical Memory I

Content

Two verbal narratives ("short stories") presented orally by the examiner. Presentation of each story requires approximately 30 seconds. Information is episodic/ verbal.

Comment on content: The first story, "Anna Thompson", describes the robbery of a woman in an urban setting and contains 67 words. The second story, "Robert Miller", relates a truck accident in a rural setting and contains 68 words. Place names of U.S. cities or regions are used in both stories. The stories have a simple lexicon, but are syntactically complex. For example, the first sentence of the "Anna Thompson" story is 37 words long and is a complex sentence with three subordinate clauses, (one of which is a compound subordinate clause), a participial phrase, and five prepositional phrases; the first sentence of the "Robert Miller" story is 25 words long and is a complex sentence with two subordinate clauses and four prepositional phrases.

Task

(1) Learn 25 units of information from each story during the initial presentation, and verbally recall the units of information immediately after presentation. (2) Retain units of information for later recall.

Basic Cognitive Requirements

Ability to attend to and comprehend task requirements; ability to attend to verbal; adequate semantic store; ability to comprehend complex syntax; adequate verbal processing speed; ability to inhibit irrelevant verbal information (inhibition of intrusions); adequate expressive language.

Memory Requirements

Recall of meaningful newly acquired verbal information.
Recall of source of information
Recall is immediate/declarative/episodic/verbal.
Retention of information units through period of delay.

Factors Contributing to Deficit Performance

Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Amnestic disorders
Aphasic disorders, receptive and expressive
Left-hemisphere dysfunction
Specific verbal learning disability

Visual Paired Associates I

Content

Six pairs of colours and abstract line drawings: colours are pink, yellow, purple, green, red, and blue; figures are closed curvilinear with solid angular block, angle with arcs, free-flowing looping line, closed curvilinear figure with loops, angular closed figure, and angular closed figure with enclosed rectangular figure. Information is episodic/visual-figural.

Task

(1) Learn conditional visual-figural associations at rate of three seconds/pair, and demonstrate recall of associations by pointing to correct colour when figural stimulus is presented.
(2) Improve learning/retention of conditional associations with repeated exposure through a minimum of three and a maximum of six learning trials.
(3) Retain conditional visual-figural associations for later recall.

Basic Cognitive Requirements

Ability to attend to and comprehend task requirements; ability to attend to visual and figural stimuli; ability to form conditional visual-figural associations; adequate visual processing speed; ability to inhibit irrelevant visual information (inhibition of intrusions).

Facilitative Cognitive Abilities

Ability to encode visual stimuli verbally; ability to use mnemonic techniques. Examples (from patients): Verbally encoding the closed curvilinear figure with loops presented with green as a "golf green" or as a map of the "Emerald Isle".

Memory Requirements

Recall of conditional visual-figural associations
Recall is immediate and long-term/declarative/
episodic/visual-figural. Comment: Time from initial presentation to last recall per set exceeds ±30 seconds, the estimated limit of immediate memory; this suggests some associations will be retrieved from long-term (secondary) memory.
Retention of conditional associations through period of delay.

Factors Contributing to Deficit Performance

Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Amnestic disorders
Specific visual learning disability
Frontal lobe dysfunction

Verbal Paired Associates I

Content

Eight word-pairs: four pairs ("easy pairs") have a semantic relationship, three pairs have categorical relationships, e.g., rose-flower, one pair is related through a prototypical characteristic, e.g., baby-cries; four pairs ("hard pairs") are arbitrarily juxtaposed without semantic relationships. Information is episodic/verbal.

Task

(1) Learn conditional verbal-verbal associations at rate of three seconds/pair, and demonstrate recall of associations by verbally presenting second word of pair when stimulus word is presented.
(2) Improve learning/retention of conditional associations with repeated exposure through a minimum of three and a maximum of six learning trials.
(3) Retain conditional verbal-verbal associations for later recall.

Basic Cognitive Requirements

Ability to attend to and comprehend task requirements; ability to attend to verbal stimuli; ability to form conditional verbal-verbal associations; adequate verbal processing speed; ability to inhibit irrelevant verbal information (inhibition of intrusions and prototypical associations); intact semantic store; mental flexibility.

Facilitative Cognitive Abilities

Ability to encode verbal stimuli visually; ability to use verbal and/or mnemonic techniques. Examples: Verbal encoding through creation of meaningful relationships, e.g., encoding school-grocery as "after *school*, I went to the *grocery* store." Visual encoding through visualization, e.g., encoding cabbage-pen by visualizing a cabbage with a ball-point pen protruding from it.

Memory Requirements

Recall of conditional visual-verbal associations
Recall is immediate and long-term/declarative/
episodic/verbal. Comment: Time from initial presentation to last recall per set exceeds ±30 seconds, the estimated limit of immediate memory; this suggests some associations will be retrieved from long-term (secondary) memory.
Retention of conditional associations through period of delay.

Factors Contributing to Deficit Performance
Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Amnestic disorders
Specific verbal learning disability
Frontal lobe dysfunction

Visual Reproduction I

Content
Four geometric designs: one design has two major figures, one with two peripheral figures and a second with a single peripheral figure. Information is episodic/ figural.

Task
(1) Learn each figure during a 10-second exposure period and demonstrate learning by drawing the figure after the stimulus card is removed.
(2) Retain figures for later recall.

Basic cognitive Requirements
Ability to attend to and comprehend task requirements; ability to attend to figural stimuli; adequate visual processing speed; ability to perceive spatial relations; ability to perceive visual detail; ability to divert and refocus attention; ability to inhibit irrelevant figural information (inhibition of intrusions); visuo-constructive ability, visual-motor integration ability;

Facilitative Cognitive Abilities
Ability to encode visual stimuli verbally.

Memory Requirements
Recall of figural stimuli.
Recall is immediate/declarative/episodic/figural.

Factors Contributing to Deficit Performance
Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Amnestic disorders
Specific visual learning disability
Apraxias
Right-hemisphere dysfunction
(Possibly left-hemisphere dysfunction)

Digit Span (Digits Forward and Digits Backward)

Content
Sequences of unrelated digits orally presented by the examiner. Digits Forward series is a minimum of 3 digits, and a maximum of 8 digits. Digits Backward series is a minimum of 2 digits and a maximum of 7 digits. Information is episodic/verbal.

Task
(1) Learn and recite series of digits in serial order.
(2) Learn series of digits and recite in reverse serial order.

Basic cognitive Requirements
Ability to attend to and comprehend task requirements; ability to attend to verbal stimuli; adequate verbal processing speed; intact temporal sequencing ability; visualization ability; mental flexibility;

Memory Requirements
Recall of verbal stimuli in correct sequential order.
Recall is immediate/declarative/episodic/verbal.

Factors Contributing to Deficit Performance
Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Amnestic disorders
Aphasic disorders
Frontal dysfunction

Visual Memory Span (Forward and Backward)
Content
(1) Eight printed red squares touched by the examiner in a predetermined sequence. Minimum sequence is two, maximum sequence is eight.
(2) Eight printed green squares touched by the examiner in a predetermined sequence. Minimum sequence is two, maximum sequence is seven.
Information is episodic/visual-spatial

Task
(1) Learn order of series and touch squares in same serial order.
(2) Learn order of series and touch squares in reverse serial order.

Basic Cognitive Requirements
Ability to attend to and comprehend task requirements; ability to attend to visual stimuli; adequate visual processing speed; intact temporal sequencing ability; visualization ability; mental flexibility;

Memory Requirements
Recall of visual stimuli in correct sequential order.
Recall is immediate/declarative/episodic/visual.

Factors Contributing to Deficit Performance
Diffuse cognitive impairment
Attention disorders
Psychiatric disorders
Amnestic disorders
Aphasic disorders
Frontal dysfunction

SUBTESTS OF DELAYED RECALL INDEX

A note on Basic Cognitive Requirements and the Delayed Recall Index: The Basic Cognitive Requirements and Facilitative Abilities listed under the "immediate" recall subtests will influence performance on the delayed recall subtests as they will limit or facilitate the initial learning and they are not repeated here. The Basic cognitive Requirements described here are those believed to make a unique contribution at the delayed recall stage.

Logical Memory II

Content

Two short verbal narratives from Logical Memory I. Information is episodic/verbal.

Task

(1) Verbally report information units from Logical Memory I or, alternatively,
(2) verbally report information units from Logical Memory I after verbal cuing.

Basic Cognitive Requirements

Ability to attend to and comprehend task requirements; ability to inhibit irrelevant information (inhibit intrusions).

Facilitative Cognitive Abilities

Ability to benefit from verbal cuing.

Memory Requirements

Recall of units of verbal information.
Recall of source of information
Recall is long-term/declarative/episodic/verbal.

Factors Contributing to Deficit Performance

All disorders/conditions listed under Logical Memory I
Specific disorders of long-term (secondary) verbal memory.

Visual Paired Associates II

Content

Stimuli from Visual Paired Associates I. Information is episodic/visual-spatial.

Task

Respond by pointing to colour associate of abstract line drawing.

Basic Cognitive Requirements

Ability to attend to and comprehend task requirements; ability to inhibit irrelevant information (inhibit intrusions).

Memory Requirements
Recall of conditional visual-figural associations.
(Alternatively, recall of verbally encoded visual-figural information.)
Recall is long-term/declarative/episodic/visual-figural.
(Alternatively, recall may be long-term/declarative/episodic/verbal.)

Factors Contributing to Deficit Performance
All disorders/conditions listed under Visual Paired Associates I.
Specific disorders of long-term (secondary) visual memory.

Verbal Paired Associates II

Content
Stimuli from Verbal Paired Associates I. Information is episodic/verbal.

Task
Respond by stating verbal associate of stimulus word.

Basic Cognitive Requirements
Ability to attend to and comprehend task requirements; ability to inhibit irrelevant information (inhibit intrusions).

Memory Requirements
Recall of conditional verbal-verbal associations.
(Alternatively, recall of visually encoded verbal information.)
Recall is long-term/declarative/episodic/verbal.
(Alternatively, recall may be long-term/declarative/episodic/visual.)

Factors Contributing to Deficit Performance
All disorders/conditions listed under Verbal Paired Associates I.
Specific disorders of long-term (secondary) verbal memory.

Visual Reproduction II

Content
Four visual designs from Visual Reproduction I. Information is episodic/figural.

Task
Draw four visual designs from Visual Reproduction I.

Basic Cognitive Requirements
Ability to attend to and comprehend task requirements; ability to inhibit irrelevant information (inhibit intrusions); visual-motor integration, visuo-constructive ability.

Memory Requirements
Recall of units figural information.
Recall of source
Recall is long-term/declarative/episodic/figural.

Factors Contributing to Deficit Performance

All disorders/conditions listed under Visual Reproduction I.
Specific disorders of long-term (secondary) figural memory.

APPENDIX 2

WMS-R INDICES AND SUBTEST MEANS FOR BIGCAT GROUPS

BIGCAT: 1.00 normal /minimal severity

Number of valid observations (listwise) = 3.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	13.75	.50	13.0	14.0	4	Wechsler Memory Scale
WMC	5.50	.58	5.0	6.0	4	WMR - Mental Control
WFM	5.75	.96	5.0	7.0	4	WMR - Figural Memory
WLM1	22.75	7.72	12.0	30.0	4	WMR- Logical Memory I
WVIPA1	5.25	5.06	1.0	11.0	4	WMR - Visual Paired A
WVEPA1	17.50	2.38	16.0	21.0	4	WMR - Verbal Paired A
WVR1	27.00	4.69	23.0	32.0	4	WMR - Visual Reproduc
WDS	14.75	2.36	13.0	18.0	4	WMR - Digit Span
WVMS	11.25	1.71	9.0	13.0	4	WMR - Visual Memory S
WLM2	16.00	7.39	9.0	25.0	4	WMR - Logical Memory
WVIPA2	3.00	2.65	1.0	6.0	3	WMR- Visual Paired As
WVEPA2	7.33	.58	7.0	8.0	3	WMR - Verbal Paired A
WVR2	15.67	13.80	.0	26.0	3	WMR - Visual Reproduc
WPL	.71	.19	.42	.83	4	WMR Percent Recall Lo
WPV	.51	.45	.0	.9	3	WMR - Percent recall
VEMI	63.00	16.67	41.0	81.0	4	WMR - Verbal Memory I
VIMI	38.00	6.83	29.0	45.0	4	WMR - Visual Memory I
GMI	101.00	20.96	78.0	126.0	4	WMR - General Memory
DRI	54.00	18.68	37.0	74.0	3	WMR - Delayed Recall
ACI	57.50	6.56	49.0	65.0	4	WMR - Attention/Conce

BIGCAT: 3.00 Alzheimers Pure/minimal severity

Number of valid observations (listwise) = 15.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.38	1.31	10.0	14.0	16	Wechsler Memory Scale
WMC	5.07	.88	4.0	6.0	15	WMR - Mental Control
WFM	4.56	2.03	1.0	8.0	16	WMR - Figural Memory
WLM1	9.75	3.19	5.0	17.0	16	WMR- Logical Memory I
WVIPA1	8.00	6.22	1.0	25.0	16	WMR - Visual Paired A
WVEPA1	9.81	4.15	1.0	17.0	16	WMR - Verbal Paired A
WVR1	23.63	6.03	12.0	34.0	16	WMR - Visual Reproduc
WDS	13.56	3.78	8.0	22.0	16	WMR - Digit Span
WVMS	11.75	2.18	7.0	15.0	16	WMR - Visual Memory S
WLM2	4.00	3.10	.0	10.0	16	WMR - Logical Memory
WVIPA2	3.50	1.67	1.0	6.0	16	WMR- Visual Paired As
WVEPA2	4.13	1.86	1.0	8.0	16	WMR - Verbal Paired A
WVR2	9.81	11.59	.0	32.0	16	WMR - Visual Reproduc
WPL	.41	.31	.00	.89	16	WMR Percent Recall Lo
WPV	.36	.39	.0	1.0	16	WMR - Percent recall
VEMI	29.31	8.62	15.0	51.0	16	WMR - Verbal Memory I
VIMI	36.19	10.09	19.0	53.0	16	WMR - Visual Memory I
GMI	65.50	15.05	42.0	87.0	16	WMR - General Memory
DRI	29.06	17.74	5.0	60.0	16	WMR - Delayed Recall
ACI	55.73	9.16	42.0	72.0	15	WMR - Attention/Conce

BIGCAT: 4.00 Alzheimer's Pure / moderate to severe
Number of valid observations (listwise) = 12.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	8.57	3.32	2.0	12.0	14	Wechsler Memory Scale
WMC	2.69	2.18	.0	6.0	13	WMR - Mental Control
WFM	3.93	2.02	.0	6.0	14	WMR - Figural Memory
WLM1	4.29	2.89	.0	10.0	14	WMR- Logical Memory I
WVIPA1	4.21	2.19	.0	7.0	14	WMR - Visual Paired A
WVEPA1	7.14	4.42	1.0	16.0	14	WMR - Verbal Paired A
WVR1	12.29	4.45	4.0	20.0	14	WMR - Visual Reproduc
WDS	9.29	1.82	7.0	12.0	14	WMR - Digit Span
WVMS	8.77	2.59	4.0	12.0	13	WMR - Visual Memory S
WLM2	1.00	1.63	.0	5.0	13	WMR - Logical Memory
WVIPA2	2.23	1.42	.0	4.0	13	WMR- Visual Paired As
WVEPA2	2.92	2.29	.0	7.0	13	WMR - Verbal Paired A
WVR2	.31	.75	.0	2.0	13	WMR - Visual Reproduc
WPL	.16	.48	-1.00	1.00	13	WMR Percent Recall Lo
WPV	.05	.14	.0	.5	13	WMR - Percent recall
VEMI	15.71	8.41	5.0	30.0	14	WMR - Verbal Memory I
VIMI	20.43	6.20	10.0	33.0	14	WMR - Visual Memory I
GMI	36.14	11.33	18.0	56.0	14	WMR - General Memory
DRI	11.62	7.83	.0	29.0	13	WMR - Delayed Recall
ACI	38.69	8.25	24.0	53.0	13	WMR - Attention/Conce

BIGCAT: 5.00 Alzheimers in combination / minimal
Number of valid observations (listwise) = 7.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	11.71	2.06	8.0	14.0	7	Wechsler Memory Scale
WMC	3.29	1.98	.0	6.0	7	WMR - Mental Control
WFM	4.43	.98	3.0	6.0	7	WMR - Figural Memory
WLM1	14.00	4.55	9.0	20.0	7	WMR- Logical Memory I
WVIPA1	7.57	3.95	3.0	15.0	7	WMR - Visual Paired A
WVEPA1	13.57	3.36	10.0	18.0	7	WMR - Verbal Paired A
WVR1	23.71	5.22	14.0	31.0	7	WMR - Visual Reproduc
WDS	13.29	4.03	7.0	18.0	7	WMR - Digit Span
WVMS	11.00	3.27	8.0	16.0	7	WMR - Visual Memory S
WLM2	7.00	5.35	.0	15.0	7	WMR - Logical Memory
WVIPA2	4.71	1.11	3.0	6.0	7	WMR- Visual Paired As
WVEPA2	5.43	1.13	4.0	7.0	7	WMR - Verbal Paired A
WVR2	6.57	2.76	2.0	10.0	7	WMR - Visual Reproduc
WPL	.44	.27	.00	.79	7	WMR Percent Recall Lo
WPV	.30	.14	.1	.5	7	WMR - Percent recall
VEMI	41.57	9.90	30.0	57.0	7	WMR - Verbal Memory I
VIMI	35.71	8.10	21.0	46.0	7	WMR - Visual Memory I
GMI	77.29	14.29	63.0	94.0	7	WMR - General Memory
DRI	33.86	6.52	21.0	42.0	7	WMR - Delayed Recall
ACI	51.86	14.85	32.0	74.0	7	WMR - Attention/Conce

BIGCAT: 6.00 Alzheimers in combination/ moderate to severe
Number of valid observations (listwise) = 2.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	13.00	.00	13.0	13.0	2	Wechsler Memory Scale
WMC	4.00	.00	4.0	4.0	2	WMR - Mental Control
WFM	4.00	.00	4.0	4.0	2	WMR - Figural Memory
WLM1	6.50	4.95	3.0	10.0	2	WMR- Logical Memory I
WVIPA1	7.00	.00	7.0	7.0	2	WMR - Visual Paired A
WVEPA1	12.50	.71	12.0	13.0	2	WMR - Verbal Paired A
WVR1	21.50	3.54	19.0	24.0	2	WMR - Visual Reproduc
WDS	9.50	.71	9.0	10.0	2	WMR - Digit Span
WVMS	11.50	.71	11.0	12.0	2	WMR - Visual Memory S
WLM2	2.50	2.12	1.0	4.0	2	WMR - Logical Memory
WVIPA2	2.50	.71	2.0	3.0	2	WMR- Visual Paired As
WVEPA2	5.00	.00	5.0	5.0	2	WMR - Verbal Paired A
WVR2	6.00	1.41	5.0	7.0	2	WMR - Visual Reproduc
WPL	.37	.05	.33	.40	2	WMR Percent Recall Lo
WPV	.29	.11	.2	.4	2	WMR - Percent recall
VEMI	25.50	9.19	19.0	32.0	2	WMR - Verbal Memory I
VIMI	32.50	3.54	30.0	35.0	2	WMR - Visual Memory I
GMI	58.00	5.66	54.0	62.0	2	WMR - General Memory
DRI	23.50	2.12	22.0	25.0	2	WMR - Delayed Recall
ACI	46.00	.00	46.0	46.0	2	WMR - Attention/Conce

BIGCAT: 7.00 Vascular Pure / minimal
Number of valid observations (listwise) = 21.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.48	1.42	9.0	14.0	25	Wechsler Memory Scale
WMC	4.65	1.43	.0	6.0	23	WMR - Mental Control
WFM	5.04	1.51	3.0	8.0	25	WMR - Figural Memory
WLM1	14.48	8.30	1.0	30.0	25	WMR- Logical Memory I
WVIPA1	8.42	3.48	3.0	16.0	24	WMR - Visual Paired A
WVEPA1	14.24	4.74	2.0	22.0	25	WMR - Verbal Paired A
WVR1	19.92	6.18	5.0	30.0	25	WMR - Visual Reproduc
WDS	13.20	3.87	8.0	22.0	25	WMR - Digit Span
WVMS	11.75	2.69	6.0	17.0	24	WMR - Visual Memory S
WLM2	8.64	7.54	.0	22.0	25	WMR - Logical Memory
WVIPA2	3.46	1.56	1.0	6.0	24	WMR- Visual Paired As
WVEPA2	5.56	1.71	3.0	8.0	25	WMR - Verbal Paired A
WVR2	8.71	6.33	.0	20.0	24	WMR - Visual Reproduc
WPL	.48	.33	.00	.95	25	WMR Percent Recall Lo
WPV	.42	.28	.0	1.0	24	WMR - Percent recall
VEMI	43.20	19.30	11.0	80.0	25	WMR - Verbal Memory I
VIMI	33.46	7.98	14.0	45.0	24	WMR - Visual Memory I
GMI	76.62	22.77	37.0	120.0	24	WMR - General Memory
DRI	35.96	14.56	16.0	69.0	23	WMR - Delayed Recall
ACI	54.48	12.04	34.0	80.0	23	WMR - Attention/Conce

BIGCAT: 8.00 Vascular Pure / moderate to severe
Number of valid observations (listwise) = 6.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	11.14	1.95	9.0	14.0	7	Wechsler Memory Scale
WMC	2.29	1.50	.0	4.0	7	WMR - Mental Control
WFM	4.83	1.47	3.0	7.0	6	WMR - Figural Memory
WLM1	10.43	6.13	2.0	18.0	7	WMR- Logical Memory I
WVIPA1	5.14	1.68	3.0	7.0	7	WMR - Visual Paired A
WVEPA1	11.14	4.98	6.0	19.0	7	WMR - Verbal Paired A
WVR1	11.29	5.22	5.0	21.0	7	WMR - Visual Reproduc
WDS	10.71	2.63	7.0	15.0	7	WMR - Digit Span
WVMS	8.57	2.23	5.0	12.0	7	WMR - Visual Memory S
WLM2	6.86	4.91	2.0	14.0	7	WMR - Logical Memory
WVIPA2	2.00	1.41	.0	3.0	7	WMR- Visual Paired As
WVEPA2	5.00	1.41	3.0	7.0	7	WMR - Verbal Paired A
WVR2	2.14	2.19	.0	5.0	7	WMR - Visual Reproduc
WPL	.67	.24	.40	1.00	7	WMR Percent Recall Lo
WPV	.23	.24	.0	.6	7	WMR - Percent recall
VEMI	32.00	15.26	13.0	53.0	7	WMR - Verbal Memory I
VIMI	21.17	6.49	13.0	31.0	6	WMR - Visual Memory I
GMI	49.67	18.95	32.0	72.0	6	WMR - General Memory
DRI	23.00	7.39	12.0	32.0	7	WMR - Delayed Recall
ACI	40.86	8.88	28.0	50.0	7	WMR - Attention/Conce

BIGCAT: 9.00 Vascular in combination / minimal
Number of valid observations (listwise) = 13.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	13.27	.96	11.0	14.0	15	Wechsler Memory Scale
WMC	4.46	1.71	1.0	6.0	13	WMR - Mental Control
WFM	5.33	.98	4.0	7.0	15	WMR - Figural Memory
WLM1	16.87	5.90	8.0	26.0	15	WMR- Logical Memory I
WVIPA1	9.00	4.26	2.0	16.0	15	WMR - Visual Paired A
WVEPA1	15.13	4.34	6.0	20.0	15	WMR - Verbal Paired A
WVR1	29.07	6.76	16.0	36.0	15	WMR - Visual Reproduc
WDS	12.80	2.73	6.0	17.0	15	WMR - Digit Span
WVMS	12.13	2.03	8.0	15.0	15	WMR - Visual Memory S
WLM2	11.40	7.70	.0	27.0	15	WMR - Logical Memory
WVIPA2	4.27	1.98	.0	6.0	15	WMR- Visual Paired As
WVEPA2	6.13	1.73	2.0	8.0	15	WMR - Verbal Paired A
WVR2	17.67	9.52	.0	33.0	15	WMR - Visual Reproduc
WPL	.63	.32	.00	1.13	15	WMR Percent Recall Lo
WPV	.58	.27	.0	1.0	15	WMR - Percent recall
VEMI	48.87	12.87	29.0	70.0	15	WMR - Verbal Memory I
VIMI	43.40	9.51	29.0	56.0	15	WMR - Visual Memory I
GMI	92.27	17.82	58.0	124.0	15	WMR - General Memory
DRI	49.87	16.61	15.0	74.0	15	WMR - Delayed Recall
ACI	53.54	9.45	39.0	66.0	13	WMR - Attention/Conce

BIGCAT: 10.00 Vascular in combinaton / moderate+
Number of valid observations (listwise) = 3.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	11.00	2.94	8.0	14.0	4	Wechsler Memory Scale
WMC	3.50	2.65	.0	6.0	4	WMR - Mental Control
WFM	4.75	.96	4.0	6.0	4	WMR - Figural Memory
WLM1	14.25	6.55	6.0	22.0	4	WMR- Logical Memory I
WVIPA1	4.75	4.35	1.0	11.0	4	WMR - Visual Paired A
WVEPA1	12.50	3.42	8.0	16.0	4	WMR - Verbal Paired A
WVR1	10.50	5.07	6.0	17.0	4	WMR - Visual Reproduc
WDS	9.75	.96	9.0	11.0	4	WMR - Digit Span
WVMS	11.33	3.06	8.0	14.0	3	WMR - Visual Memory S
WLM2	12.00	5.48	4.0	16.0	4	WMR - Logical Memory
WVIPA2	3.50	2.65	.0	6.0	4	WMR- Visual Paired As
WVEPA2	5.25	1.50	4.0	7.0	4	WMR - Verbal Paired A
WVR2	5.25	7.09	.0	15.0	4	WMR - Visual Reproduc
WPL	.83	.16	.67	1.00	4	WMR Percent Recall Lo
WPV	.35	.43	.0	.9	4	WMR - Percent recall
VEMI	41.00	14.83	24.0	60.0	4	WMR - Verbal Memory I
VIMI	20.00	8.16	14.0	32.0	4	WMR - Visual Memory I
GMI	61.00	22.54	38.0	92.0	4	WMR - General Memory
DRI	34.75	15.92	21.0	57.0	4	WMR - Delayed Recall
ACI	46.33	10.79	34.0	54.0	3	WMR - Attention/Conce

BIGCAT: 11.00 Mixed SDAT Vascular / minimal
Number of valid observations (listwise) = 2.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	11.33	2.89	8.0	13.0	3	Wechsler Memory Scale
WMC	3.50	3.54	1.0	6.0	2	WMR - Mental Control
WFM	5.33	1.53	4.0	7.0	3	WMR - Figural Memory
WLM1	12.00	10.54	2.0	23.0	3	WMR- Logical Memory I
WVIPA1	6.00	1.00	5.0	7.0	3	WMR - Visual Paired A
WVEPA1	16.33	7.09	10.0	24.0	3	WMR - Verbal Paired A
WVR1	22.00	6.08	18.0	29.0	3	WMR - Visual Reproduc
WDS	8.67	1.53	7.0	10.0	3	WMR - Digit Span
WVMS	12.67	6.43	8.0	20.0	3	WMR - Visual Memory S
WLM2	7.33	9.45	.0	18.0	3	WMR - Logical Memory
WVIPA2	3.00	2.65	.0	5.0	3	WMR- Visual Paired As
WVEPA2	4.67	2.52	2.0	7.0	3	WMR - Verbal Paired A
WVR2	9.33	14.47	.0	26.0	3	WMR - Visual Reproduc
WPL	.38	.39	.00	.78	3	WMR Percent Recall Lo
WPV	.34	.49	.0	.9	3	WMR - Percent recall
VEMI	40.33	28.15	14.0	70.0	3	WMR - Verbal Memory I
VIMI	33.33	6.66	29.0	41.0	3	WMR - Visual Memory I
GMI	73.67	34.49	43.0	111.0	3	WMR - General Memory
DRI	32.00	32.19	6.0	68.0	3	WMR - Delayed Recall
ACI	38.50	10.61	31.0	46.0	2	WMR - Attention/Conce

BIGCAT: 12.00 Mixed SDAT Vascular / moderate+
Number of valid observations (listwise) = 6.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	10.13	2.75	5.0	13.0	8	Wechsler Memory Scale
WMC	2.87	2.47	.0	6.0	8	WMR - Mental Control
WFM	5.14	2.12	1.0	7.0	7	WMR - Figural Memory
WLM1	6.63	6.12	.0	16.0	8	WMR- Logical Memory I
WVIPA1	6.00	2.27	3.0	10.0	8	WMR - Visual Paired A
WVEPA1	8.50	3.12	4.0	13.0	8	WMR - Verbal Paired A
WVR1	14.00	8.64	4.0	31.0	8	WMR - Visual Reproduc
WDS	9.13	3.40	4.0	15.0	8	WMR - Digit Span
WVMS	11.17	1.94	8.0	13.0	6	WMR - Visual Memory S
WLM2	3.37	4.03	.0	10.0	8	WMR - Logical Memory
WVIPA2	1.83	1.47	.0	4.0	6	WMR- Visual Paired As
WVEPA2	3.50	1.87	1.0	6.0	6	WMR - Verbal Paired A
WVR2	4.00	7.51	.0	19.0	6	WMR - Visual Reproduc
WPL	.28	.68	-1.00	1.33	8	WMR Percent Recall Lo
WPV	.29	.42	.0	1.0	6	WMR - Percent recall
VEMI	21.75	13.21	8.0	45.0	8	WMR - Verbal Memory I
VIMI	24.71	10.66	16.0	45.0	7	WMR - Visual Memory I
GMI	48.43	17.23	26.0	67.0	7	WMR - General Memory
DRI	19.17	13.61	6.0	39.0	6	WMR - Delayed Recall
ACI	42.83	6.21	37.0	52.0	6	WMR - Attention/Conce

BIGCAT: 13.00 Frontal Pure / minimal
Number of valid observations (listwise) = 24.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.17	1.79	6.0	14.0	24	Wechsler Memory Scale
WMC	4.25	1.89	.0	6.0	24	WMR - Mental Control
WFM	5.08	1.64	1.0	8.0	24	WMR - Figural Memory
WLM1	14.79	5.46	4.0	26.0	24	WMR- Logical Memory I
WVIPA1	8.42	4.23	4.0	16.0	24	WMR - Visual Paired A
WVEPA1	15.67	4.23	5.0	21.0	24	WMR - Verbal Paired A
WVR1	22.54	7.67	5.0	34.0	24	WMR - Visual Reproduc
WDS	11.04	2.07	7.0	15.0	24	WMR - Digit Span
WVMS	11.79	2.65	7.0	16.0	24	WMR - Visual Memory S
WLM2	9.42	4.66	1.0	19.0	24	WMR - Logical Memory
WVIPA2	3.08	1.93	.0	6.0	24	WMR- Visual Paired As
WVEPA2	6.04	1.30	4.0	8.0	24	WMR - Verbal Paired A
WVR2	10.38	8.35	.0	26.0	24	WMR - Visual Reproduc
WPL	.63	.21	.13	1.00	24	WMR Percent Recall Lo
WPV	.42	.31	.0	1.1	24	WMR - Percent recall
VEMI	45.25	13.14	20.0	71.0	24	WMR - Verbal Memory I
VIMI	36.04	10.13	15.0	51.0	24	WMR - Visual Memory I
GMI	81.29	17.69	44.0	108.0	24	WMR - General Memory
DRI	38.04	14.22	17.0	66.0	24	WMR - Delayed Recall
ACI	49.92	9.31	34.0	68.0	24	WMR - Attention/Conce

BIGCAT: 14.00 Frontal Pure / moderate+

Number of valid observations (listwise) = .00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.00	.	12.0	12.0	1	Wechsler Memory Scale
WMC	.00	.	.0	.0	1	WMR - Mental Control
WFM	2.00	.	2.0	2.0	1	WMR - Figural Memory
WLM1	9.00	.	9.0	9.0	1	WMR- Logical Memory I
WVIPA1	2.00	.	2.0	2.0	1	WMR - Visual Paired A
WVEPA1	13.00	.	13.0	13.0	1	WMR - Verbal Paired A
WVR1	10.00	.	10.0	10.0	1	WMR - Visual Reproduc
WDS	6.00	.	6.0	6.0	1	WMR - Digit Span
WVMS	Variable is missing for every case.					WMR - Visual Memory S
WLM2	8.00	.	8.0	8.0	1	WMR - Logical Memory
WVIPA2	3.00	.	3.0	3.0	1	WMR- Visual Paired As
WVEPA2	7.00	.	7.0	7.0	1	WMR - Verbal Paired A
WVR2	.00	.	.0	.0	1	WMR - Visual Reproduc
WPL	.89	.	.89	.89	1	WMR Percent Recall Lo
WPV	.00	.	.0	.0	1	WMR - Percent recall
VEMI	31.00	.	31.0	31.0	1	WMR - Verbal Memory I
VIMI	14.00	.	14.0	14.0	1	WMR - Visual Memory I
GMI	45.00	.	45.0	45.0	1	WMR - General Memory
DRI	28.00	.	28.0	28.0	1	WMR - Delayed Recall
ACI	Variable is missing for every case.					WMR - Attention/Conce

BIGCAT: 17.00 Depression /minimal

Number of valid observations (listwise) = 16.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	13.41	.94	11.0	14.0	17	Wechsler Memory Scale
WMC	5.00	1.17	2.0	6.0	17	WMR - Mental Control
WFM	6.29	1.31	4.0	8.0	17	WMR - Figural Memory
WLM1	19.72	7.49	.0	32.0	18	WMR- Logical Memory I
WVIPA1	10.67	4.10	4.0	17.0	18	WMR - Visual Paired A
WVEPA1	17.00	5.03	6.0	24.0	18	WMR - Verbal Paired A
WVR1	31.61	7.68	7.0	39.0	18	WMR - Visual Reproduc
WDS	13.83	3.43	8.0	19.0	18	WMR - Digit Span
WVMS	14.72	2.30	11.0	18.0	18	WMR - Visual Memory S
WLM2	14.44	5.54	.0	20.0	18	WMR - Logical Memory
WVIPA2	5.06	1.00	4.0	6.0	18	WMR- Visual Paired As
WVEPA2	6.56	2.01	1.0	8.0	18	WMR - Verbal Paired A
WVR2	25.00	10.56	.0	38.0	18	WMR - Visual Reproduc
WPL	.64	.44	-1.00	.94	18	WMR Percent Recall Lo
WPV	.76	.27	.0	1.0	18	WMR - Percent recall
VEMI	56.44	17.36	6.0	82.0	18	WMR - Verbal Memory I
VIMI	50.24	7.35	34.0	63.0	17	WMR - Visual Memory I
GMI	107.65	22.67	47.0	145.0	17	WMR - General Memory
DRI	62.67	18.70	14.0	82.0	18	WMR - Delayed Recall
ACI	62.29	9.62	44.0	76.0	17	WMR - Attention/Conce

BIGCAT: 19.00 Other / minimal
Number of valid observations (listwise) = 22.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.48	1.94	5.0	14.0	25	Wechsler Memory Scale
WMC	5.04	1.36	.0	6.0	23	WMR - Mental Control
WFM	5.78	1.99	2.0	10.0	27	WMR - Figural Memory
WLM1	16.61	6.91	2.0	33.0	28	WMR- Logical Memory I
WVIPA1	10.04	4.86	1.0	17.0	28	WMR - Visual Paired A
WVEPA1	14.75	4.64	6.0	23.0	28	WMR - Verbal Paired A
WVR1	27.86	8.01	9.0	40.0	28	WMR - Visual Reproduc
WDS	13.21	3.52	6.0	22.0	28	WMR - Digit Span
WVMS	12.26	2.46	7.0	17.0	27	WMR - Visual Memory S
WLM2	11.00	7.23	.0	27.0	28	WMR - Logical Memory
WVIPA2	4.25	1.96	.0	6.0	28	WMR- Visual Paired As
WVEPA2	5.86	2.07	.0	8.0	28	WMR - Verbal Paired A
WVR2	17.32	10.12	1.0	37.0	28	WMR - Visual Reproduc
WPL	.59	.30	.00	.94	28	WMR Percent Recall Lo
WPV	.61	.29	.1	1.1	28	WMR - Percent recall
VEMI	47.96	16.14	16.0	85.0	28	WMR - Verbal Memory I
VIMI	44.19	11.23	17.0	63.0	27	WMR - Visual Memory I
GMI	93.00	22.13	51.0	129.0	27	WMR - General Memory
DRI	48.54	18.23	13.0	79.0	28	WMR - Delayed Recall
ACI	56.91	10.11	30.0	78.0	22	WMR - Attention/Conce

BIGCAT: 20.00 Other / moderate+
Number of valid observations (listwise) = 7.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	10.25	3.24	4.0	13.0	8	Wechsler Memory Scale
WMC	2.00	1.93	.0	6.0	8	WMR - Mental Control
WFM	4.60	1.58	2.0	8.0	10	WMR - Figural Memory
WLM1	10.20	6.30	2.0	21.0	10	WMR- Logical Memory I
WVIPA1	6.60	3.44	.0	12.0	10	WMR - Visual Paired A
WVEPA1	9.70	5.33	1.0	19.0	10	WMR - Verbal Paired A
WVR1	15.60	7.85	1.0	26.0	10	WMR - Visual Reproduc
WDS	9.90	4.04	5.0	17.0	10	WMR - Digit Span
WVMS	10.56	4.45	4.0	19.0	9	WMR - Visual Memory S
WLM2	4.90	5.38	.0	17.0	10	WMR - Logical Memory
WVIPA2	3.20	2.25	.0	6.0	10	WMR- Visual Paired As
WVEPA2	4.20	1.81	1.0	7.0	10	WMR - Verbal Paired A
WVR2	5.20	5.98	.0	17.0	10	WMR - Visual Reproduc
WPL	.38	.32	.00	.83	10	WMR Percent Recall Lo
WPV	.30	.30	.0	.8	10	WMR - Percent recall
VEMI	30.10	15.98	5.0	54.0	10	WMR - Verbal Memory I
VIMI	26.80	10.82	5.0	40.0	10	WMR - Visual Memory I
GMI	56.90	18.56	27.0	76.0	10	WMR - General Memory
DRI	24.90	14.16	10.0	52.0	10	WMR - Delayed Recall
ACI	38.14	15.52	18.0	68.0	7	WMR - Attention/Conce

APPENDIX 3

WMS-R INDICES AND SUBTEST MEANS FOR NEWCAT GROUPS

NEWCAT: 1.00 [NORMAL]
Number of valid observations (listwise) = 3.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	13.75	.50	13.0	14.0	4	Wechsler Memory Scale
WMC	5.50	.58	5.0	6.0	4	WMR - Mental Control
WFM	5.75	.96	5.0	7.0	4	WMR - Figural Memory
WLM1	22.75	7.72	12.0	30.0	4	WMR- Logical Memory I
WVIPA1	5.25	5.06	1.0	11.0	4	WMR - Visual Paired A
WVEPA1	17.50	2.38	16.0	21.0	4	WMR - Verbal Paired A
WVR1	27.00	4.69	23.0	32.0	4	WMR - Visual Reproduc
WDS	14.75	2.36	13.0	18.0	4	WMR - Digit Span
WVMS	11.25	1.71	9.0	13.0	4	WMR - Visual Memory S
WLM2	16.00	7.39	9.0	25.0	4	WMR - Logical Memory
WVIPA2	3.00	2.65	1.0	6.0	3	WMR- Visual Paired As
WVEPA2	7.33	.58	7.0	8.0	3	WMR - Verbal Paired A
WVR2	15.67	13.80	.0	26.0	3	WMR - Visual Reproduc
WPL	.71	.19	.42	.83	4	WMR Percent Recall Lo
WPV	.51	.45	.0	.9	3	WMR - Percent recall
VEMI	63.00	16.67	41.0	81.0	4	WMR - Verbal Memory I
VIMI	38.00	6.83	29.0	45.0	4	WMR - Visual Memory I
GMI	101.00	20.96	78.0	126.0	4	WMR - General Memory
DRI	54.00	18.68	37.0	74.0	3	WMR - Delayed Recall
ACI	57.50	6.56	49.0	65.0	4	WMR - Attention/Conce

NEWCAT: 3.00 [DAT-C (M)]
Number of valid observations (listwise) = 22.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.17	1.56	8.0	14.0	23	Wechsler Memory Scale
WMC	4.50	1.54	.0	6.0	22	WMR - Mental Control
WFM	4.52	1.75	1.0	8.0	23	WMR - Figural Memory
WLM1	11.04	4.07	5.0	20.0	23	WMR- Logical Memory I
WVIPA1	7.87	5.54	1.0	25.0	23	WMR - Visual Paired A
WVEPA1	10.96	4.24	1.0	18.0	23	WMR - Verbal Paired A
WVR1	23.65	5.68	12.0	34.0	23	WMR - Visual Reproduc
WDS	13.48	3.76	7.0	22.0	23	WMR - Digit Span
WVMS	11.52	2.50	7.0	16.0	23	WMR - Visual Memory S
WLM2	4.91	4.04	.0	15.0	23	WMR - Logical Memory
WVIPA2	3.87	1.60	1.0	6.0	23	WMR- Visual Paired As
WVEPA2	4.52	1.75	1.0	8.0	23	WMR - Verbal Paired A
WVR2	8.83	9.80	.0	32.0	23	WMR - Visual Reproduc
WPL	.42	.29	.00	.89	23	WMR Percent Recall Lo
WPV	.34	.33	.0	1.0	23	WMR - Percent recall
VEMI	33.04	10.52	15.0	57.0	23	WMR - Verbal Memory I
VIMI	36.04	9.34	19.0	53.0	23	WMR - Visual Memory I
GMI	69.09	15.52	42.0	94.0	23	WMR - General Memory
DRI	30.52	15.21	5.0	60.0	23	WMR - Delayed Recall
ACI	54.50	11.06	32.0	74.0	22	WMR - Attention/Conce

NEWCAT: 4.00 [DAT-C (M-S)]
Number of valid observations (listwise) = 14.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	9.13	3.44	2.0	13.0	16	Wechsler Memory Scale
WMC	2.87	2.07	.0	6.0	15	WMR - Mental Control
WFM	3.94	1.88	.0	6.0	16	WMR - Figural Memory
WLM1	4.56	3.08	.0	10.0	16	WMR- Logical Memory I
WVIPA1	4.56	2.25	.0	7.0	16	WMR - Visual Paired A
WVEPA1	7.81	4.51	1.0	16.0	16	WMR - Verbal Paired A
WVR1	13.44	5.28	4.0	24.0	16	WMR - Visual Reproduc
WDS	9.31	1.70	7.0	12.0	16	WMR - Digit Span
WVMS	9.13	2.59	4.0	12.0	15	WMR - Visual Memory S
WLM2	1.20	1.70	.0	5.0	15	WMR - Logical Memory
WVIPA2	2.27	1.33	.0	4.0	15	WMR- Visual Paired As
WVEPA2	3.20	2.24	.0	7.0	15	WMR - Verbal Paired A
WVR2	1.07	2.15	.0	7.0	15	WMR - Visual Reproduc
WPL	.19	.45	-1.00	1.00	15	WMR Percent Recall Lo
WPV	.08	.16	.0	.5	15	WMR - Percent recall
VEMI	16.94	8.84	5.0	32.0	16	WMR - Verbal Memory I
VIMI	21.94	7.15	10.0	35.0	16	WMR - Visual Memory I
GMI	38.88	13.01	18.0	62.0	16	WMR - General Memory
DRI	13.20	8.39	.0	29.0	15	WMR - Delayed Recall
ACI	39.67	8.06	24.0	53.0	15	WMR - Attention/Conce

NEWCAT: 7.00 [VAS-C (M)]
Number of valid observations (listwise) = 34.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.77	1.31	9.0	14.0	40	Wechsler Memory Scale
WMC	4.58	1.52	.0	6.0	36	WMR - Mental Control
WFM	5.15	1.33	3.0	8.0	40	WMR - Figural Memory
WLM1	15.37	7.50	1.0	30.0	40	WMR- Logical Memory I
WVIPA1	8.64	3.75	2.0	16.0	39	WMR - Visual Paired A
WVEPA1	14.57	4.56	2.0	22.0	40	WMR - Verbal Paired A
WVR1	23.35	7.74	5.0	36.0	40	WMR - Visual Reproduc
WDS	13.05	3.46	6.0	22.0	40	WMR - Digit Span
WVMS	11.90	2.44	6.0	17.0	39	WMR - Visual Memory S
WLM2	9.67	7.62	.0	27.0	40	WMR - Logical Memory
WVIPA2	3.77	1.75	.0	6.0	39	WMR- Visual Paired As
WVEPA2	5.78	1.72	2.0	8.0	40	WMR - Verbal Paired A
WVR2	12.15	8.79	.0	33.0	39	WMR - Visual Reproduc
WPL	.53	.33	.00	1.13	40	WMR Percent Recall Lo
WPV	.48	.28	.0	1.0	39	WMR - Percent recall
VEMI	45.33	17.22	11.0	80.0	40	WMR - Verbal Memory I
VIMI	37.28	9.79	14.0	56.0	39	WMR - Visual Memory I
GMI	82.64	22.14	37.0	124.0	39	WMR - General Memory
DRI	41.45	16.67	15.0	74.0	38	WMR - Delayed Recall
ACI	54.14	11.04	34.0	80.0	36	WMR - Attention/Conce

NEWCAT: 8.00 [VAS-C (M-S)]
Number of valid observations (listwise) = 9.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	11.09	2.21	8.0	14.0	11	Wechsler Memory Scale
WMC	2.73	1.95	.0	6.0	11	WMR - Mental Control
WFM	4.80	1.23	3.0	7.0	10	WMR - Figural Memory
WLM1	11.82	6.26	2.0	22.0	11	WMR- Logical Memory I
WVIPA1	5.00	2.72	1.0	11.0	11	WMR - Visual Paired A
WVEPA1	11.64	4.34	6.0	19.0	11	WMR - Verbal Paired A
WVR1	11.00	4.92	5.0	21.0	11	WMR - Visual Reproduc
WDS	10.36	2.16	7.0	15.0	11	WMR - Digit Span
WVMS	9.40	2.67	5.0	14.0	10	WMR - Visual Memory S
WLM2	8.73	5.50	2.0	16.0	11	WMR - Logical Memory
WVIPA2	2.55	1.97	.0	6.0	11	WMR- Visual Paired As
WVEPA2	5.09	1.38	3.0	7.0	11	WMR - Verbal Paired A
WVR2	3.27	4.52	.0	15.0	11	WMR - Visual Reproduc
WPL	.73	.22	.40	1.00	11	WMR Percent Recall Lo
WPV	.27	.31	.0	.9	11	WMR - Percent recall
VEMI	35.27	15.05	13.0	60.0	11	WMR - Verbal Memory I
VIMI	20.70	6.78	13.0	32.0	10	WMR - Visual Memory I
GMI	54.20	20.08	32.0	92.0	10	WMR - General Memory
DRI	27.27	12.00	12.0	57.0	11	WMR - Delayed Recall
ACI	42.50	9.24	28.0	54.0	10	WMR - Attention/Conce

NEWCAT: 12.00 [MIX-(M-S)]
Number of valid observations (listwise) = 8.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	10.45	2.70	5.0	13.0	11	Wechsler Memory Scale
WMC	3.00	2.49	.0	6.0	10	WMR - Mental Control
WFM	5.20	1.87	1.0	7.0	10	WMR - Figural Memory
WLM1	8.09	7.40	.0	23.0	11	WMR- Logical Memory I
WVIPA1	6.00	1.95	3.0	10.0	11	WMR - Visual Paired A
WVEPA1	10.64	5.50	4.0	24.0	11	WMR - Verbal Paired A
WVR1	16.18	8.58	4.0	31.0	11	WMR - Visual Reproduc
WDS	9.00	2.93	4.0	15.0	11	WMR - Digit Span
WVMS	11.67	3.64	8.0	20.0	9	WMR - Visual Memory S
WLM2	4.45	5.72	.0	18.0	11	WMR - Logical Memory
WVIPA2	2.22	1.86	.0	5.0	9	WMR- Visual Paired As
WVEPA2	3.89	2.03	1.0	7.0	9	WMR - Verbal Paired A
WVR2	5.78	9.73	.0	26.0	9	WMR - Visual Reproduc
WPL	.31	.60	-1.00	1.33	11	WMR Percent Recall Lo
WPV	.30	.41	.0	1.0	9	WMR - Percent recall
VEMI	26.82	18.87	8.0	70.0	11	WMR - Verbal Memory I
VIMI	27.30	10.14	16.0	45.0	10	WMR - Visual Memory I
GMI	56.00	24.72	26.0	111.0	10	WMR - General Memory
DRI	23.44	20.40	6.0	68.0	9	WMR - Delayed Recall
ACI	41.75	6.90	31.0	52.0	8	WMR - Attention/Conce

NEWCAT: 13.00 [FRONT (M)]
Number of valid observations (listwise) = 24.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.17	1.79	6.0	14.0	24	Wechsler Memory Scale
WMC	4.25	1.89	.0	6.0	24	WMR - Mental Control
WFM	5.08	1.64	1.0	8.0	24	WMR - Figural Memory
WLM1	14.79	5.46	4.0	26.0	24	WMR- Logical Memory I
WVIPA1	8.42	4.23	4.0	16.0	24	WMR - Visual Paired A
WVEPA1	15.67	4.23	5.0	21.0	24	WMR - Verbal Paired A
WVR1	22.54	7.67	5.0	34.0	24	WMR - Visual Reproduc
WDS	11.04	2.07	7.0	15.0	24	WMR - Digit Span
WVMS	11.79	2.65	7.0	16.0	24	WMR - Visual Memory S
WLM2	9.42	4.66	1.0	19.0	24	WMR - Logical Memory
WVIPA2	3.08	1.93	.0	6.0	24	WMR- Visual Paired As
WVEPA2	6.04	1.30	4.0	8.0	24	WMR - Verbal Paired A
WVR2	10.38	8.35	.0	26.0	24	WMR - Visual Reproduc
WPL	.63	.21	.13	1.00	24	WMR Percent Recall Lo
WPV	.42	.31	.0	1.1	24	WMR - Percent recall
VEMI	45.25	13.14	20.0	71.0	24	WMR - Verbal Memory I
VIMI	36.04	10.13	15.0	51.0	24	WMR - Visual Memory I
GMI	81.29	17.69	44.0	108.0	24	WMR - General Memory
DRI	38.04	14.22	17.0	66.0	24	WMR - Delayed Recall
ACI	49.92	9.31	34.0	68.0	24	WMR - Attention/Conce

NEWCAT: 17.00 [DEPR (M)]
Number of valid observations (listwise) = 16.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	13.41	.94	11.0	14.0	17	Wechsler Memory Scale
WMC	5.00	1.17	2.0	6.0	17	WMR - Mental Control
WFM	6.29	1.31	4.0	8.0	17	WMR - Figural Memory
WLM1	19.72	7.49	.0	32.0	18	WMR- Logical Memory I
WVIPA1	10.67	4.10	4.0	17.0	18	WMR - Visual Paired A
WVEPA1	17.00	5.03	6.0	24.0	18	WMR - Verbal Paired A
WVR1	31.61	7.68	7.0	39.0	18	WMR - Visual Reproduc
WDS	13.83	3.43	8.0	19.0	18	WMR - Digit Span
WVMS	14.72	2.30	11.0	18.0	18	WMR - Visual Memory S
WLM2	14.44	5.54	.0	20.0	18	WMR - Logical Memory
WVIPA2	5.06	1.00	4.0	6.0	18	WMR- Visual Paired As
WVEPA2	6.56	2.01	1.0	8.0	18	WMR - Verbal Paired A
WVR2	25.00	10.56	.0	38.0	18	WMR - Visual Reproduc
WPL	.64	.44	-1.00	.94	18	WMR Percent Recall Lo
WPV	.76	.27	.0	1.0	18	WMR - Percent recall
VEMI	56.44	17.36	6.0	82.0	18	WMR - Verbal Memory I
VIMI	50.24	7.35	34.0	63.0	17	WMR - Visual Memory I
GMI	107.65	22.67	47.0	145.0	17	WMR - General Memory
DRI	62.67	18.70	14.0	82.0	18	WMR - Delayed Recall
ACI	62.29	9.62	44.0	76.0	17	WMR - Attention/Conce

NEWCAT: 19.00 [OTHER (M)]
Number of valid observations (listwise) = 22.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	12.48	1.94	5.0	14.0	25	Wechsler Memory Scale
WMC	5.04	1.36	.0	6.0	23	WMR - Mental Control
WFM	5.78	1.99	2.0	10.0	27	WMR - Figural Memory
WLM1	16.61	6.91	2.0	33.0	28	WMR- Logical Memory I
WVIPA1	10.04	4.86	1.0	17.0	28	WMR - Visual Paired A
WVEPA1	14.75	4.64	6.0	23.0	28	WMR - Verbal Paired A
WVR1	27.86	8.01	9.0	40.0	28	WMR - Visual Reproduc
WDS	13.21	3.52	6.0	22.0	28	WMR - Digit Span
WVMS	12.26	2.46	7.0	17.0	27	WMR - Visual Memory S
WLM2	11.00	7.23	.0	27.0	28	WMR - Logical Memory
WVIPA2	4.25	1.96	.0	6.0	28	WMR- Visual Paired As
WVEPA2	5.86	2.07	.0	8.0	28	WMR - Verbal Paired A
WVR2	17.32	10.12	1.0	37.0	28	WMR - Visual Reproduc
WPL	.59	.30	.00	.94	28	WMR Percent Recall Lo
WPV	.61	.29	.1	1.1	28	WMR - Percent recall
VEMI	47.96	16.14	16.0	85.0	28	WMR - Verbal Memory I
VIMI	44.19	11.23	17.0	63.0	27	WMR - Visual Memory I
GMI	93.00	22.13	51.0	129.0	27	WMR - General Memory
DRI	48.54	18.23	13.0	79.0	28	WMR - Delayed Recall
ACI	56.91	10.11	30.0	78.0	22	WMR - Attention/Conce

NEWCAT: 20.00 [OTHER (M-S)]
Number of valid observations (listwise) = 7.00

Variable	Mean	Std Dev	Minimum	Maximum	Valid N	Label
WIO	10.44	3.09	4.0	13.0	9	Wechsler Memory Scale
WMC	1.78	1.92	.0	6.0	9	WMR - Mental Control
WFM	4.36	1.69	2.0	8.0	11	WMR - Figural Memory
WLM1	10.09	5.99	2.0	21.0	11	WMR- Logical Memory I
WVIPA1	6.18	3.54	.0	12.0	11	WMR - Visual Paired A
WVEPA1	10.00	5.16	1.0	19.0	11	WMR - Verbal Paired A
WVR1	15.09	7.63	1.0	26.0	11	WMR - Visual Reproduc
WDS	9.55	4.01	5.0	17.0	11	WMR - Digit Span
WVMS	10.56	4.45	4.0	19.0	9	WMR - Visual Memory S
WLM2	5.18	5.19	.0	17.0	11	WMR - Logical Memory
WVIPA2	3.18	2.14	.0	6.0	11	WMR- Visual Paired As
WVEPA2	4.45	1.92	1.0	7.0	11	WMR - Verbal Paired A
WVR2	4.73	5.88	.0	17.0	11	WMR - Visual Reproduc
WPL	.43	.34	.00	.89	11	WMR Percent Recall Lo
WPV	.27	.30	.0	.8	11	WMR - Percent recall
VEMI	30.18	15.16	5.0	54.0	11	WMR - Verbal Memory I
VIMI	25.64	10.97	5.0	40.0	11	WMR - Visual Memory I
GMI	55.82	17.97	27.0	76.0	11	WMR - General Memory
DRI	25.18	13.47	10.0	52.0	11	WMR - Delayed Recall
ACI	38.14	15.52	18.0	68.0	7	WMR - Attention/Conce